Attachment B to Comments on Chapter 7 – Carcinogenic Effects

Philip Morris Comment on 1996 External Review Draft

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COMMENTS ON:

CARCINOGENIC EFFECTS OF EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE

EXCERPT: ETS AND LUNG CANCER

California Environmental Protection Agency
Reproductive and Cancer Hazard Assessment Section
Office of Environmental Health Hazard Assessment

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SECTION I: OVERVIEW AND INTRODUCTION

In the January 1996 external review draft, "Carcinogenic Effects of Exposure to Environmental Tobacco Smoke -- Excerpt: ETS and Lung Cancer" (hereinafter, the Excerpt), Cal/EPA contends that recently published epidemiologic studies support the conclusions reached in the U.S. EPA's 1993 Risk Assessment on environmental tobacco smoke (ETS). This contention is incorrect and is not supported by the data.

In this written comment, it will be well documented that the present draft of the Excerpt is a superficial treatment of the claimed association between ETS exposure and lung cancer risk. (Section II) Cal/EPA selectively cites and interprets studies and data in an attempt to support a conclusion that the recent epidemiologic data agree with the positions espoused in the U.S. EPA Risk Assessment on ETS.

Further, this comment will highlight and summarize a number of the unresolved criticisms of the U.S. EPA Risk Assessment on ETS, showing that the assumption that that document was a conclusive, thorough review of the literature is unfounded. (Section III) In particular, data on ETS chemistry, ETS exposure data, the limitations of questionnaire data, animal inhalation studies and genotoxicity data were not adequately addressed.

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Finally, since Cal/EPA relies almost exclusively on the epidemiologic literature in reaching its conclusions, this comment will address a number of epidemiologic issues that were treated in insufficient detail in the Excerpt. (Section IV)

Given the shortcomings of the Excerpt, this comment concludes that Cal/EPA's stated position is not adequately supported. Specifically, when **all** of the relevant data are considered, those data **do not support the claim that ETS exposure is associated with an increased risk of lung cancer in nonsmokers.**

Based on the information contained herein and upon publicly available information, Cal/EPA should defer from taking any further action on this assessment of risks.

- To avoid "bad science," the Cal/EPA report should await the recommendations of the OEHHA Risk Assessment Advisory Committee. Cal/EPA Secretary James Strock has been quoted as saying that "scientifically sound risk assessments are the foundation upon which wise environmental decisions are made," which implies an obligation to assure that this report is sound science.

  (i) The California Legislature has also recognized the significant impact of risk assessments. In 1993, the

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Legislature enacted S.B. 1082 (Cal. Health & Safety Code sec. 57004), which required the director of Cal/EPA's Office of Environmental Health Hazard Assessment (OEHHA) to convene an advisory committee "to conduct a comprehensive review of the policies, methods, and guidelines to be followed by the state for the identification and assessment of chemical toxicity." The Advisory Committee was convened in 1994. It has held seven meetings; the next meeting will be held on April 10 and 11, 1996. At the same time that the work of the Advisory Committee is nearing completion, Cal/EPA is attempting to produce a formal risk assessment concerning ETS, complete with conclusions that may be calculated to command attention in the press but may be easily misinterpreted as to their true significance.

Given the universally recognized need for thorough and reasonable risk assessment guidelines,[1] it is difficult to see how Cal/EPA would now allow the release of any risk assessment without a determination that the assessment followed the recommendations of the Advisory

1. For example, note the current ongoing work of President Clinton's Commission on Risk Assessment and Risk Management (scheduled to issue a report on April 24, 1996) and the ongoing work of the U.S. Environmental Protection Agency to issue Revised Carcinogen Risk Assessment Guidelines.

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Committee. Publishing an incomplete and unreviewed ETS assessment now has the potential of eclipsing the State's stated commitment to uniform, sound risk assessment practices.

- As developed more fully herein, Cal/EPA cannot take any action based on reliance upon U.S. EPA's Risk Assessment. Cal/EPA should not rely upon U.S. EPA's Risk Assessment on ETS, and in so doing, avoid the necessary and required original work by Cal/EPA. Under the California Health and Safety Code, 539660(c), Cal/EPA must evaluate the "quality of data" underlying any health evaluation. Cal/EPA cannot and should not pursue any report which relies upon EPA's Risk Assessment.

- Cal/EPA's ETS risk assessment (and specifically the lung cancer sub chapter) should not be pursued because Cal/EPA lacks the requisite authority to pursue such work. Cal/EPA's risk assessment on ETS was initiated prior to the enactment of AB 13, which imposed a state-wide ban on smoking in most places in California. See Labor Code sec. 6404.5(b). The restrictions of AB 13 encompass most nonresidential areas in the state, and even where smoking is restricted to designated areas, AB 13 requires ventilation equipment meeting specified standards to ensure that the air is not recirculated but exhausted outside. Even prior to AB 13, the Proposition 65

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Scientific Advisory Panel listed ETS as a carcinogen. As a result, in those areas where limited smoking is allowed, Proposition 65 requires that warnings be posted to alert persons of their potential exposure to ETS. Given the existence of AB 13 and Proposition 65, and given the authority of the California Occupational Safety and Health Administration to generally regulate worker health and safety it is difficult to see any basis of authority for Cal/EPA to pursue a risk assessment concerning ETS.

- Cal/EPA should decline to take any further action on the ETS risk assessment given the extensive regulatory work already underway at the U.S. Occupational Safety and Health Administration (OSHA). Not only does Cal/EPA lack authority to pursue an ETS risk assessment, but if there were a current compelling need to review ETS issues, that need is being met by U.S. OSHA. Federal OSHA has completed the public comment phase of the lengthiest, most extensive regulatory hearing and review of potential ETS effects ever conducted. The agency held six months of public hearings, amassed more than 110,000 comments from interested parties and scientific experts, and collected extensive studies and data regarding the claimed health effects of exposure to ETS. Unlike the brief Cal/EPA workshops, the federal OSHA hearings were conducted as part of federal OSHA's regulatory responsibility for determining

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- Reissue Chapter 7 of the Cal/EPA assessment in its entirety, as the new table of contents indicates some changes from the chapter on "other cancers" issued in May 1994.

- Substantially broaden the scope of its literature review to include all relevant materials. In particular, Cal/EPA should consider the public record compiled in response to U.S. OSHA's rulemaking on indoor air quality, which contains a vast amount of literature as well as perhaps the most recent and comprehensive analyses of ETS issues, many of which are cited herein.

- Given the unresolved criticisms of the U.S. EPA Risk Assessment on ETS, not rely on that document and its analyses, but obtain the relevant literature and re-analyze it. That is, Cal/EPA must "start from the beginning." In this regard, the agency should obtain and analyze the underlying data -- particularly the data from the Fontham, et al., study.

- Abandon the selective approach taken in the present draft of the Excerpt, and clearly define the criteria used in evaluating data and delineate the rationale for its approaches, in order to reduce the appearance of subjectivity.

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- Revise and reissue in draft all other chapters in this assessment of ETS risks, to incorporate the suggestions inherent in the foregoing as to all chapters.

- Review the Congressional Research Service Report. Most of Cal/EPA's overall risk assessment does not have the benefit of the November 1995 Congressional Research Service (CRS) report on ETS which raised serious questions about the methodology of the U.S. EPA's ETS risk assessment. The CRS study was not addressed in Cal/EPA's most recently released draft excerpt.

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SECTION II: CAL/EPA'S REVIEW IS SUBJECTIVE, SELECTIVE AND UNSCIENTIFIC

Cal/EPA's Excerpt clearly appears to be designed to support the conclusion that ETS exposure is associated with an increased lung cancer risk. The following discussion will illustrate a number of specific examples of subjectivity and selectivity in the Excerpt.

A. Cal/EPA Frequently Engages in Selective Reporting

Cal/EPA selectively references studies and reports data from studies in a manner that strengthens its positions. One example of this selectivity is found in the citation of the "first" studies to be published on spousal smoking and lung cancer. Cal/EPA cites only the Hirayama[1] and Trichopoulos, et al.,[2] studies, published in 1981. (p. 8) This statement is incomplete. Also in 1981, Garfinkel published data from a large cohort study conducted in the United States.[3] Unlike the Hirayama and Trichopoulos studies, Garfinkel's data support no **increased lung cancer risk associated with ETS exposure.** The failure to include the Garfinkel (1981) study -- whether intentional or an oversight -- gives the appearance that it was omitted because it did not support the theme being developed by Cal/EPA.

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Elsewhere, Cal/EPA claims that U.S. EPA's Risk Assessment on ETS is the "most recent" meta-analysis of the epidemiologic data on ETS exposure and lung cancer. (p. 8) This is inaccurate -- the results of several meta-analyses that fail to support U.S. EPA's conclusions have subsequently been published.[4-10] Again, the omission of these references contributes to the impression that Cal/EPA is not presenting a thorough, complete representation of the scientific literature, and is instead focusing only on material that supports its conclusions.

Cal/EPA is also guilty of selectively reporting data from individual epidemiologic studies. For example, in the discussion of childhood ETS exposure, Cal/EPA references a reported risk for "high exposure" during childhood of 2.07 (95% CI 1.16-3.68) from the Janerich, et al., study. This is the **only** statistically significant association reported in that study.[11] Not only could a single statistically significant risk estimate have arisen by chance, given the number of analyses reported in that paper, but taking that result out of context misrepresents the Janerich, et al., study. Cal/EPA could just as well have highlighted the workplace risk estimate from the Janerich, et al., study, 0.91 (95% CI 0.80-1.04) in the Excerpt's workplace discussion -- but it did not.

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Similarly, Cal/EPA selectively reports other data on workplace ETS exposures and lung cancer risk. Only two studies have reported workplace risk estimates that are statistically significant.[12,13] The vast majority of workplace risk estimates are not statistically significant.[11,14-25] While this is evident from the table of workplace results in the Excerpt, the text does not make this clear. Nor does the text indicate that recent meta-analyses of the workplace data report a summary risk estimate of approximately 1.0, consistent with no increase nor decrease in risk.[4,5]

Cal/EPA also engages in "data-dredging" in discussing the workplace data. Namely, it creates a subcategory of three studies "in which the assessment of workplace exposure to ETS was complete," (p. 18) and claims that those studies are "generally supportive of an association between workplace ETS exposure and risk of lung cancer." (p. 18) However, Table 7.7 of the Excerpt shows that only one of the three risk estimates, that of Fontham, et al., is statistically significant. The workplace risk estimates for the other two studies cited to support Cal/EPA's proposition (Wu, 1985, and Wu-Williams, et al., 1990) are not statistically significant, and thus do not clearly support an association, contrary to the Cal/EPA's claim.

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The review of workplace data by Cal/EPA appears to be an attempt by the agency to "make something out of nothing," because, as noted previously, meta-analyses of the workplace data consistently show no association.

Cal/EPA's discussion of the epidemiologic data on reported ETS exposures from sources other than the spouse is also flawed, because it relies in large part on only the reported results of the four most recent studies, rather than discussing the data presented in **all** the studies on this topic. As reported in a recent comprehensive review of the ETS-lung cancer literature, the data on lung cancer risks for non-spousal ETS exposures, taken as a whole, provide "little or no substantial evidence of an association."[26] Cal/EPA's approach to the data effectively ignores such analyses.

B. The Excerpt Contains Misleading Statements

There are a number of instances in the Excerpt where statements are framed in such a manner as to yield misleading impressions. Cal/EPA must draft its document so that its meaning is clear.

For instance, on p. 8, Cal/EPA states: "In order to gain a more accurate estimate of the association between ETS exposure

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and lung cancer, a meta-analysis approach has been used to pool results of **comparable** studies." (emphasis added) This statement implies that the spousal smoking studies are "comparable," when it has been clearly illustrated that they are not.[26] Moreover, it implies that meta-analysis may be appropriately applied to these studies, which is not a universally accepted position.[27]

On the same page, the Excerpt states: "Most of the individual studies found a small increased risk." (p. 8) Actually, of the 40 studies presently available,[1-3,11-18,20-25,28-30] only eight report statistically significantly increased overall risk estimates for spousal smoking and lung cancer.[1,2,13,18,25,35,41,42] The vast majority -- 80 percent -- of the spousal smoking studies report overall risk estimates that are not statistically significant. Without statistical significance, a reportedly increased risk is compatible with the null hypothesis of no association. Thus, Cal/EPA's reference to a "small increased risk" is misleading.

Another example of misleading reporting is found in Cal/EPA's treatment of the Fontham, et al., study. Cal/EPA states that cotinine measurements were obtained for 81 percent of self-respondent cases. (p. 15) The choice of this percentage is misleading. Fontham, et al. (1994), state: "Urine samples were analyzed for 356 (53.5%) of 665 cases and 1064 (83.3%) of 1278 controls."[13] Thus, cotinine samples were available for only about

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half of all the cases in the study, according to the original report. Here, Cal/EPA's choice of the value to cite seems to be intended to portray the Fontham, et al., study's methods in the most favorable light.

In another section discussing the Fontham, et al., study, Cal/EPA states: "[T]he U.S. multicenter study corroborated the subjects' self-reported current nonsmoking status using the urinary cotinine level." (p. 21) While Cal/EPA acknowledges that cotinine measurements assess **only** current smoking, it accepts the misclassification rates of 0.6 percent in cases and 2.3 percent in controls reported by Fontham, et al., as accurate. The Excerpt does not mention that Fontham, et al., measured cotinine in hospitalized cases. The vast majority of hospitals severely restrict smoking (in fact, accreditation requires that smoking be banned); moreover, many lung cancer patients who happen to be smokers stop smoking after diagnosis. Thus, the cotinine measurements in this study do not even give a good indication of present smoking status, let alone previous long-term smoking status. The smoking status misclassification rates portrayed by Fontham, et al., as accurate are, in reality, **not** representative of the true situation. As reported by Lee and Forey, a review of the literature indicates that smoking status misclassification rates may range as high as 15 to 20 percent.[21]

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C. **Cal/EPA Fails to Provide Justification for Considering the Recent Epidemiologic Studies Separately from the U.S. EPA Risk Assessment**

One of the most curious omissions in the Excerpt is its failure to discuss the outcome of a U.S. EPA-style meta-analysis in which data from the four epidemiologic studies published since 1991 are included. Cal/EPA provides no justification for this omission. Given Cal/EPA's acceptance (and even defense) of the U.S. EPA meta-analysis, the failure to consider a meta-analysis including all the studies can be interpreted as an attempt to exclude an analysis that would not support Cal/EPA's conclusions.

A review of the scientific literature reveals several post-EPA meta-analyses conducted by other researchers.[4,7-10] These meta-analyses illustrate that, if the U.S. EPA's approach is adopted, inclusion of new studies lowers the overall summary risk estimate.

For instance, in a recent paper, LeVois and Layard report:[4]

> Using the EPA's methods and assumptions, we have calculated a summary relative risk of 1.07 from a meta-analysis of 13 U.S. female spousal smoking studies, including these two recent studies [Brownson, et al., and Stockwell, et al.] This relative risk, with

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> 95% confidence interval of 0.95-1.21, is not statistically significant.

The inclusion of two additional recent studies in the meta-analysis effectively reversed the conclusion of the U.S. EPA Risk Assessment on ETS. The summary relative risk is no longer statistically significant, and, therefore, does not support a conclusion of an association between spousal smoking and lung cancer.

Gross (1995) noted that when Kabat (1990, an initial report of the study discussed in the Excerpt[32]), Stockwell, et al.,[22] and Brownson, et al.,[14] are included in a U.S. EPA-type meta-analysis, a summary risk estimate of 1.12 (95% CI 0.99-1.27) is calculated -- prior to adjustment for smoking status misclassification.[7] Gross states: "Since any such adjustment lowers the relative risk, it implies the null hypothesis of no association cannot be rejected." In another 1995 paper, Gross provides the misclassification-adjusted summary risk estimate; even when the U.S. EPA's very low rate of 1 percent is used, the summary value is 1.07 (95% CI 0.95-1.21).[8]

Similarly, Gori (1994) observes that, while he does not endorse the U.S. EPA approach:[9]

> Including the two latest studies [Brownson and Stockwell] explicitly excluded from the EPA's review and using the EPA's own [adjustment]

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> procedure, a realistic correction [for misclassification] of only 2.5% would nullify any excess risk estimates in the meta-analysis of the 13 available U.S. studies of spousal exposure.

Gori states that the published literature suggests smoking status misclassification rates between two and 10 percent (average four to five percent), compared to the 1.09 percent used by U.S. EPA.[9]

Sugita, et al., also reanalyzed the U.S. spousal smoking data, incorporating the Stockwell, et al., and Brownson, et al., studies, and calculated a summary risk estimate for the U.S. studies of 1.10 (95% CI 0.97-1.26).[10] Based on this and other summary risk estimates calculated by Sugita, et al., they conclude:

> From these odds ratios it has not been demonstrated scientifically whether or not ETS is a particular risk factor for lung cancer. The conclusion that the relationship between exposure to ETS and lung cancer is weak remains unchanged. (p. 180)

It seems clear that Cal/EPA facilitated its arguably predetermined conclusion by simply making observations about the "concordance" or "similarity" of the recent studies to U.S. EPA's conclusions, rather than by conducting its own statistical analysis. Cal/EPA should explain why the approach of comparing the individual post-1991 studies to the U.S. EPA summary risk estimate

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was chosen instead of incorporating the new studies into a meta-analysis or other, more formal, comparison.

Cal/EPA should also provide further explanation for its position that the recent studies support the U.S. EPA's conclusion, given that the Congressional Research Service reached the following conclusion, based on a review of the same material:[53]

> The new studies, including the very large Brownson study, did not clarify the existence of a risk. Indeed, they complicated the interpretation of the evidence, since the two largest U.S. studies -- Fontham and Brownson -- found in one case a positive risk that was barely statistically significant and the other no risk at all. (p. 25)

D. Subjective Terms Are Used Throughout the Excerpt Without Definition

Throughout the Excerpt, Cal/EPA employs terms like "concordance" (p. 7), "very similar to" (p. 7), "closest to" (p. 7), "consistency" (p. 27), "similar" (p. 14), and "compatible" (p. 19) when discussing the results of two or more studies or analyses. Because these terms are not defined, their scientific meaning is unknown to readers of the Excerpt, who are therefore left with the impression that these terms are subjective descriptions without a rigorous scientific basis.

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For example, Cal/EPA states: "Results from the largest population-based study, conducted in several metropolitan areas of the U.S. (Fontham et al., 1994) were **closest to** the pooled estimate of the U.S. EPA report." (p. 7) (emphasis added) The subjective phrase "closest to" has no scientific meaning. Used in this manner, it appears to be a transparent attempt to bolster the position that the newer studies support the conclusions of the U.S. EPA Risk Assessment, without conducting a statistical analysis.

E. The Excerpt Contains Unreferenced and Poorly Referenced Claims

In the Executive Summary of the Excerpt, Cal/EPA claims that there is "compelling biologic plausibility of an effect of ETS on lung cancer." (p. 7) No references are cited in support of this proposition. Thus, the public may take this statement at face value, when the statement is actually not supported by a review of the relevant scientific literature. Neither animal inhalation studies nor genotoxicity studies provide support for the claim, as discussed elsewhere in this submission (Section III).

Similarly, Cal/EPA provides only one reference for its claim that "there is no publication bias against statistically nonsignificant results on ETS in the peer-reviewed literature." (p. 10) The issue of publication bias cannot be summed up by a

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single reference; Cal/EPA should review additional literature on this issue, including the literature on meta-analysis, where much of the debate on publication bias has developed.

Moreover, Cal/EPA does not address the issues of selective reporting and "data-dredging," another form of bias common in epidemiologic studies. For instance, the Fontham, et al., study reports more than 100 case-control comparisons.[13] With this many comparisons, a number of statistically significant associations would arise by chance alone. This issue is not adequately addressed in the original studies, nor in the Excerpt.

F. Cal/EPA's Reanalysis of Kabat, et al. (1995), Is Not Justified

Cal/EPA's analysis of the 1995 Kabat, et al., case-control study[17] certainly gives the appearance of a bias toward reporting results that support the position that the recent ETS epidemiologic studies support the conclusions of the 1993 U.S. EPA Risk Assessment on ETS. In fact, the approach taken by Cal/EPA has already been deemed "controversial" by observers.[54]

The risk estimates based on the Kabat, et al., data, as originally reported in the publication, do not agree with Cal/EPA's position. As Kabat and colleagues stated: "[T]he pattern of odds

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ratios [in this study] shows little indication of an association of environmental tobacco smoke with lung cancer in nonsmokers."[17]

After noting that "[t]here were no significant associations between spouses' smoking and risk of lung cancer in male or female subjects" in the original report of the Kabat, et al., study, Cal/EPA states: **"We calculated the OR for lung cancer in males and females combined to be 1.19 (95% CI=0.76-1.87) in association with spousal ETS exposure."** (p. 18) (emphasis added) Cal/EPA then summarizes its conclusions: "Although [Kabat et al.] . . . *interpreted their findings* (analyzing men and women separately) to be unsupportive of an association between ETS exposure and risk of lung cancer, the odds ratio we calculated from their results, though not statistically significant, was in fact very similar to the pooled estimate from the U.S. EPA report." (p. 19)

Because the author gives no statistical or scientific justification for combining the Kabat, et al., data for men and women, this approach appears to be an attempt to "make the data fit." The decision to combine the male and female data is even more curious when one considers that the U.S. EPA Risk Assessment based its conclusions on data for women only, completely ignoring the available data on males, which, taken as a whole, support no increase in lung cancer risk in men whose wives smoked.[36] Moreover,

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the Excerpt implies that there is some importance in the reanalysis of the Kabat, et al., yielding a risk estimate of 1.19, the same as the U.S. EPA summary risk estimate, when this simple coincidence has little, if any, real meaning.

The interpretation by Kabat, et al., that their data do not support an association between ETS exposure and lung cancer risk is wholly appropriate. Kabat and colleagues report a number of risk estimates that do not achieve statistical significance. They also exercise caution in interpreting the few statistically significant risk estimates in their study. However, Cal/EPA does not simply accept this interpretation, apparently since it does not support Cal/EPA's position. Interestingly, Cal/EPA makes no comment about the unsupported interpretation by Brownson, et al., of the data in their case-control study.[14]

An examination of the reported results in the Brownson, et al., study shows that the overall risk estimate for spousal smoking is 1.0 (95% CI 0.8-1.2), clearly inconsistent with an increase in risk. The only statistically significant results in the Brownson paper were restricted to "qualitative" indices of exposure, where study subjects provided an "estimate [of] a perceived level" of exposure.[14] Despite the vast majority of the data being consistent with no increase in risk, Brownson, et al., concluded:

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> [O]ur study and others conducted during the past decade suggest a small but consistent elevation in the risk of lung cancer in nonsmokers due to passive smoking.

According to a scientist who has reviewed and reanalyzed the Brownson publication and the raw data from the study, "influences directed to the identification and reporting of an association between ETS [exposure] and lung cancer may have affected the reporting of the results" from this study and others.[55]

G. Conclusion

As the lung cancer Excerpt is written, it appears to be an attempt by Cal/EPA to make recent data agree with the conclusions of the U.S. EPA Risk Assessment on ETS. The selectivity and subjectivity of the Cal/EPA discussion lead to conclusions which simply are not supported by the data and objective, thorough scientific analyses.

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SECTION III: CAL/EPA RELIES INAPPROPRIATELY ON THE U.S. EPA RISK ASSESSMENT ON ETS, WITHOUT SUFFICIENT ATTENTION TO THE DEMONSTRATED FLAWS IN THAT DOCUMENT

Cal/EPA relies extensively on the 1993 U.S. EPA Risk Assessment on ETS, which purportedly reviewed the literature on ETS and lung cancer through 1991.[1] Cal/EPA has apparently accepted the U.S. EPA Risk Assessment as conclusive. While mention is made of certain criticisms of the U.S. EPA document (e.g., pp. 9-10), Cal/EPA simply lists those criticisms, without providing sufficient rebuttal. Cal/EPA sums up its discussion of the U.S. EPA Risk Assessment by stating: "[T]he U.S. EPA's report is based on the total weight of evidence, and not on an individual study." (p. 10) The following discussion will show that (i) the criticisms leveled against the U.S. EPA report are much more severe than the superficial treatment by Cal/EPA would imply, and (ii) U.S. EPA omitted a large amount of relevant data and information in reaching its conclusions about ETS, so that the "weight of the evidence" claim is misleading.

A. Criticisms of the U.S. EPA Risk Assessment Have Never Been Adequately Addressed by the Agency

Criticisms have been raised about the U.S. EPA's Risk Assessment since the initial release of a draft for public review in 1990. At that time, independent scientists and interested parties raised concerns about many important issues; over 100

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submissions were made to the U.S. EPA public comment docket. The numerous criticisms of the 1990 draft were summarized in a document prepared for the Agency, which stated:[2]

> The predominant theme in comments related to lung cancer is that the classification of ETS as a Group A carcinogen, causally related to increased risk of lung cancer, is unwarranted. . . . The claim that it is biologically plausible that ETS is a lung carcinogen is contentious and unjustified in the Report. (pp. 3-4)
>
> It is not possible to summarize comprehensively in just a few pages the remarks from the thousands of pages of comments submitted. (p. 4)

The criticisms -- on toxicological, chemistry, exposure, epidemiologic and statistical issues -- raised with respect to the 1990 draft of the U.S. EPA Risk Assessment were not adequately addressed in the revised draft that was issued in 1992. At that time, comments were again submitted by a number of independent scientists and other interested parties. In addition to reiterating many of the criticisms initially raised, and confirming that those criticisms were not adequately addressed in the new draft, the comments also raised new issues related to the second review draft.

Following the release of the final document in January 1993, essentially identical to the heavily criticized 1992 draft,

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a number of articles critical of the Risk Assessment have appeared in the scientific press.[3-9] For instance, Huber and colleagues (1993) wrote:[3]

> [T]he EPA's risk assessment is built on the manipulation of data, ignores critical chemical analyses and key epidemiological data, violates time-honored statistical principles, fails to control adequately for important confounding influences (factors other than the one studied that may affect a result or conclusion) that provide alternative explanations for its conclusions, and violates its own guidelines for assessing and establishing risk to a potential environmental toxin. It lacks credible quality control and adequate external unbiased peer review. **In short, in its report on ETS, the EPA did not comply with accepted principles of toxicology, chemistry, and epidemiology, nor with its own guidelines for undertaking cancer risk assessment. In fact, the conclusions drawn by the EPA are not even supported by the EPA's own statements.** (p. 45) (emphasis added)

In a 1994 commentary on the U.S. EPA Risk Assessment, Gori stated:[4]

> [T]his figure [3,000 deaths] is . . . the **result of an unprecedented exercise in data manipulation.** Among other unjustifiable gambits, this EPA report stands out for its unorthodox insistence on one-tailed statistics and 90% confidence intervals, for arbitrary and unproven adjustment procedures, and for its selective use of epidemiologic evidence. For instance, without explanation the report has summarily excluded workplace data and the latest epidemiologic studies, which together void the report's conclusions when added to the body of evidence. (emphasis added)

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Furthermore, in another discussion published in 1995, Gori observed:[5]

> EPA claims to have used a weight of evidence approach. In reality, ETS has been characterized only indirectly by an analogy to active smoking that EPA itself discounts. Negative epidemiologic reports were summarily ignored. Statistical standards were relaxed. Competing and well-known risk factors were disregarded. Documented misclassification biases were discounted. **By its own admission, EPA made very selective use of available studies, emphasizing only those that support its preconceived conclusions.** (pp. 20-21) (emphasis added)

In a technical analysis, Gross (1995) illustrated clearly that the U.S. EPA methodology for calculating deaths purportedly attributable to ETS exposure "is **far from an exact or even approximate science**. . . . [M]inor to moderate changes in the model parameters lead to large changes in the estimated number of [deaths]."[6] (p. 411) (emphasis added) Further, he stated that "EPA has not given very much thought to the uncertainty of its estimates," and noted that the epidemiologic data on ETS and lung cancer are consistent with a risk estimate of 1.0, which, in U.S. EPA's model, would yield an estimate of zero "attributable" deaths.

More recently, the Congressional Research Service (CRS) has issued two reports that raise substantial questions about the

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U.S. EPA Risk Assessment.[10,11] In 1994, one of the authors of the 1994 CRS review, Jane Gravelle, described the conclusions of that document as follows:[12]

> [O]ur evaluation was that **the statistical evidence does not appear to support a conclusion that there are substantial health effects of passive smoking.** (emphasis added)

A compilation of materials criticizing or questioning the U.S. EPA Risk Assessment is submitted as Appendix I to this comment.

B. Data on ETS Chemistry Were Omitted from the U.S. EPA Risk Assessment

The U.S. EPA Risk Assessment failed to discuss or even to reference a significant amount of relevant literature on the physical and chemical properties of ETS.

A number of scientists have concluded that ETS is not the same as either mainstream or sidestream smoke.[13-17] ETS is an aged and diluted mixture of sidestream and exhaled mainstream smoke; ETS is a dynamic, ever-changing mixture that undergoes chemical transformations and physical changes as it ages and is diluted in the air.[13-15] As one researcher in tobacco smoke chemistry has observed, "there are profound physical and quantitative chemical

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differences" among the three kinds of smoke (mainstream smoke, sidestream smoke and ETS).[13]

Studies also indicate that constituents in ETS are **hundreds to thousands** of times more dilute than either sidestream or mainstream smoke.[16,17] Concentrations of ETS constituents in real-life situations are often below the limits of detection and measurement for even the most sensitive air monitors. Often, the contributions of ETS constituents to the ambient air are indistinguishable from background levels of the same constituents generated by other sources.[16]

The strategy of comparing mainstream and sidestream smoke employed by U.S. EPA in the Risk Assessment (e.g., Chapter 3) ignores the profound effect of dilution in the ambient air upon tobacco smoke constituents. As two tobacco smoke chemists report:[14]

> The important question is not the ratio of sidestream/mainstream but rather what is the concentration of the constituent in the indoor environment and how does it compare to levels from sources other than ETS. Studies based solely on observations of fresh sidestream, or highly and unrealistically concentrated ETS should take into account the possible differences between these smokes and ETS found in real life situations.

Similarly, the 1986 Report of the Surgeon General notes: "SS [sidestream smoke] characteristics, as measured in chambers, do not

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represent those of ETS, as inhaled by the nonsmoker under non-experimental conditions."[18]

C. Data on Measurements of ETS Exposure Were Omitted from the U.S. EPA Risk Assessment

Cal/EPA focuses heavily on the epidemiologic literature in the Excerpt. In failing to mention the literature on issues of ETS exposure, Cal/EPA seems to be implying that the U.S. EPA Risk Assessment provides sufficient discussion of these issues, which is not the case.

The initial public review draft for the U.S. EPA Risk Assessment (1990) did not even contain an exposure assessment. Comments submitted to the public docket for the 1990 draft risk assessment observed that U.S. EPA had failed to provide an exposure assessment that considered data from the numerous published studies on actual levels of ETS constituents in the air of public places and workplaces. In apparent response to that criticism, the revised 1992 draft of the U.S. EPA Risk Assessment contained a chapter entitled "Estimation of Environmental Tobacco Smoke Exposure," but the chapter's authors failed to consider at least 35 pertinent exposure studies on ETS constituent levels in public places.

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Furthermore, during its review of the chapter in July of 1992, the U.S. EPA Science Advisory Board rejected the chapter and returned it to the author for rewriting. Nevertheless, without either an exposure assessment or recourse to any of the data pertaining to it, the Science Advisory Board endorsed U.S. EPA's estimate of exposure and risk for the entire U.S. population. A revised chapter on ETS exposure occurs in the final U.S. EPA Risk Assessment; however, the studies and data therein are not integrated into the U.S. EPA Risk Assessment.

Only a small number of actual ETS exposure studies available in the published literature are even discussed in the U.S. EPA Risk Assessment. Many of the studies of exposure to ETS constituents under realistic conditions in public places, workplaces and homes omitted from the U.S. EPA Risk Assessment report minimal exposures to ETS; these reported exposures do not support the conclusions of the U.S. EPA Risk Assessment.[17,19-62]

For instance, studies on ambient measures of nicotine in offices and restaurants report average levels of approximately 2.0 and 3.5 ug/m^3 nicotine, respectively. These exposures are equivalent to 1/400 to 1/200 of the nicotine found in a single cigarette. Averages for nonsmoking areas in workplaces with smoking restrictions are even lower, averaging less than 1 ug/m^3 nicotine, or about 1/1,000 of the nicotine in a single cigarette.

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This means that the typical nonsmoking worker would have to spend from 200 to more than 1,000 hours in an office, restaurant or public place in order to be exposed to the nicotine equivalent of a single cigarette.[35,55-58]

The cigarette equivalent approach has been criticized because different results would be obtained if different reference compounds are chosen. These criticisms are based simply on calculating the sidestream/mainstream ratios for the different reference compounds. Such a calculation would be accurate if there were no chemical and physical changes which occur when sidestream smoke is transformed into ETS. This, as has already been clearly pointed out earlier in this submission, is not the case. As a consequence, it would not be at all correct to state that a typical nonsmoking worker who spends 200 to 1,000 hours in an office, restaurant or public place is exposed to the **smoke** equivalent of one cigarette, since ETS is not at all chemically or physically identical to the smoke to which a smoker is exposed.

With regard to the calculation of cigarette equivalents based on other reference compounds, it is important to note that the vast majority of ETS constituents are found, generally in much greater amounts, in indoor environments in the absence of ETS. Researchers report that there is little difference in ambient levels of carbon monoxide or nitrogen oxides in smoking and

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nonsmoking areas of workplaces and public places and in homes with or without smokers.[16,27,30,31,49,59,60] Similarly, levels of volatile organic compounds such as formaldehyde and benzene in the presence of smoking are often indistinguishable from levels reported in nonsmoking areas.[16,32,35,50-52] Studies that have examined ETS constituent levels of nitrosamines also report minimal contributions to overall ambient air levels in homes, offices and public places.[48,61,62]

D. Limitations of Exposure Estimates Based on Questionnaires Were Not Discussed by U.S. EPA

The "exposure" estimates in epidemiologic studies on ETS are wholly independent of a large body of data on ambient exposure measurements to various constituents of ETS, which, taken as a whole, suggests that ETS exposures are minimal. The epidemiologic studies rely on questionnaire data, the accuracy of which depends on an individual's ability to recall past events, such as how much a husband smoked in the past 20 to 30 years.[63-65] The two bodies of data, epidemiologic/health effects, on the one hand, and exposure measurements on the other, have never been integrated into one comprehensive study.

In a 1994 article critical of the U.S. EPA Risk Assessment, Gori wrote:

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> A major limitation of epidemiologic studies on ETS has been the unreliable estimates of dose, which compound the uncertainties of personal or proxy recall of the intensity, frequency, and duration of exposures over individual lifetimes. Even the simple dichotomous classification of exposed and non-exposed subjects presents recognized uncertainties, such as those deriving from the self-classification of some smokers as non-smokers. (p. 327)

U.S. EPA relied heavily on the epidemiologic data in its Risk Assessment on ETS, without adequately exploring the limitations of questionnaire data.

1. "Spousal Smoking" Is Not Equivalent to ETS Exposure

A fundamental problem with Cal/EPA's Excerpt and with U.S. EPA's Risk Assessment is the **uncritical** acceptance of the risks reported in spousal smoking studies as **true** risks due to **exposure to ETS**. The central question is whether or not "ETS exposure" is the same thing as "spousal smoking"; that is, does living with a smoker imply exposure to ETS?

Even though U.S. EPA concedes that spousal smoking status is a "crude measure" of ETS exposure and one that is "prone to exposure misclassification,"[66] the Agency nevertheless equates spousal smoking status with household exposures to ETS.[67] However, the extent to which the spousal smoking index is an accurate,

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reliable and valid quantitative indicator of ETS exposure was not assessed by U.S. EPA in its Risk Assessment. The quality of the underlying exposure data from the spousal smoking studies is thus of critical importance for epidemiologic studies on ETS and chronic disease, because "the accuracy of any statistical analysis is limited by the accuracy of the information upon which it is based."[68]

The spousal smoking index is not an accurate marker for exposure to ETS. That "marriage to a smoker" is **not** equivalent to home exposures to ETS has been demonstrated in two studies.[69,70] Friedman, et al., polled nearly 38,000 nonsmokers and ex-smokers in California about ETS exposure. Nearly 35 percent of respondents classified by their spouse's smoking status reported no exposure overall to ETS; 47 percent of women married to smokers reported zero hours of exposure at home.[69] The researchers concluded that "using the spouse's smoking status to classify persons resulted, as far as can be discovered with our relatively crude questionnaire, in a considerable amount of [exposure] misclassification."[69]

A 1994 published study conducted in the U.K. reports a similar conclusion.[70] The researchers compared subjective estimates of ETS exposure with objective measurements of airborne ETS markers via personal monitors (breathing zone measurements). They reported that 45 percent of subjects with a smoking partner assessed their

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exposure as "none or low." Similarly, 30 to 40 percent of individuals married to smokers were actually exposed to less than the average ETS levels measured among subjects with a nonsmoking partner. The researchers conclude: "Clearly, spousal smoking status would not be a reliable means to assess the ETS exposure of individuals or small groups of subjects."[70]

Thus, "marriage to a smoker" may -- or may not -- imply exposure to ETS; it cannot serve as an accurate, quantitative surrogate for actual exposure measurements.

2. Attempts to "Refine" the Spousal Smoking Index Do Not Yield Better Data

In attempting to "refine" the spousal smoking index, a number of spousal smoking studies have employed exposure estimates beyond the simple index of "marriage to a smoker."[65,71] Questions regarding ETS exposures have included those related to the **intensity** of exposure (e.g., the number of smokers in the home or the number of cigarettes smoked per day or per year), or the **duration** of exposure (e.g., hours of exposure, years of marriage to a smoker or years of smoke exposure).[71] Estimates of the intensity or duration of spousal smoking exposure are derived by questionnaire or interview of the study subject (the case) or next of kin.[72]

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There is no standardized or validated questionnaire available for use in epidemiologic studies on ETS, and no single questionnaire was used in the published studies on spousal smoking.[73] As a consequence, definitions of various ETS exposure indices have differed considerably from study to study with respect to source, intensity and duration.

3. Questionnaire Responses Are Neither Reliable Nor Accurate

The questionnaire, by its very nature, can provide only a crude, qualitative estimate of exposure. Questionnaire data do not, and cannot, provide information on **concentration** (e.g., actual levels of airborne ETS constituents) or **frequency** of ETS exposure. As the U.S. National Academy of Sciences observed in 1991: "Exposures [to ETS] occur at a wide range of concentrations for highly variable periods and in numerous indoor environments. Unlike active smoking, exposure to ETS cannot now be easily assessed. . . ."[73] The questionnaire is thus only an indirect means of assessing exposure. This, according to a NIOSH witness at the U.S. OSHA Public Hearing, is one of "the principal weaknesses in the epidemiologic evidence to date."[74]

Where exposure is defined as "concentration over time" or "intensity, frequency and duration," the questionnaire's inherent shortcomings are obvious. Thus, Coultas, et al., note:[75]

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> Questionnaires on exposure to environmental tobacco smoke generally assess the strength of the source, e.g., the number of smokers, the number of cigarettes consumed and the duration of exposure. The concentration of environmental tobacco smoke, however, depends not only on the source strength, but on room size, mixing, adsorption of smoke components, and the rate of exchange of indoor with outdoor air. Personal exposure also varies with the nonsmoker's proximity to the smoker. Questionnaires cannot comprehensively and accurately assess each of these factors.

Estimates of "intensity" and "duration" of exposure also depend upon respondent memories of literally decades of potential exposure scenarios. Complete recall, of course, is impossible, and even partial recall may be faulty. For example, studies indicate that while spouses (or children) may generally agree in reporting a partner's (or parent's) smoking status (i.e., whether or not a spouse smoked), agreement regarding the amount smoked or duration of smoking is often very poor.[63,65,76-79]

Pron, et al., examined the reliability of self-reported ETS exposure histories by interviewing and re-interviewing study subjects.[65] Consistency of responses about exposure between initial interview and re-interview was poor, and correlations between responses were low, especially for questions related to intensity and duration of exposure. The authors conclude:

> [T]his is the first study to assess the reliability of information reported on passive smoke exposures in personal interviews. Test-

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retest estimates of reliability suggest that misclassification of such exposure may be extensive.

In "An Assessment of the Validity of Questionnaire Responses Provided by a Surviving Spouse,"[76] Lerchen and Samet report that wives generally agree with the smoking status classification given by their spouse, but that 44 percent of the spouses could not provide a detailed smoking history of the spouse. The authors observed that wives tended to report that their spouse smoked 20 cigarettes per day, even when the husbands reported that they smoked substantially more or less. The researchers remarked that "the validity of such surrogate information, when available, is uncertain." Kolonel, et al., reported similar results in 1977.[80]

Sandler and Shore investigated the degree of agreement on parental smoking status from interviews of parents and their (adult) children.[77] These authors reported reasonable agreement in responses about the smoking status of the parent, but agreement on exposure level estimates was extremely poor. The authors conclude that childhood ETS exposure information obtained via questionnaire from adults "cannot readily be used to estimate levels of exposure" to ETS, and that "data on levels of exposure were not of high enough quality to allow for detailed evaluation of dose-response."[77]

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4. Questionnaire Responses Are Influenced by Perceptions

Reconstruction of a life history of ETS exposure is highly influenced by recall accuracy -- imagine recalling, with **any** degree of accuracy, the duration, frequency and degree of personal ETS exposure over the previous week, year or decade, or during a marriage, during adulthood, etc. Studies suggest that even **recent perceptions** of ETS exposure may be wholly inadequate indicators of **actual** ETS exposures.[64,70,81-83]

O'Connor, et al., compared self-reported exposures to ETS with ambient levels of nicotine collected by personal monitoring devices.[81] Thirty-six percent of women who reported ETS exposure by questionnaire were misclassified as "exposed" to ETS according to objective measures of exposure.

Coultas, et al., in a study of 10 homes, found that questionnaire responses about ETS exposures "were poor predictors of concentrations of respirable particles and nicotine."[64] Similarly, a workplace study conducted by Schenker, et al., reported no association between respirable nicotine concentrations and self-reported exposures to ETS.[82] The authors conclude that "self-reported exposure to ETS is an inaccurate measure of passive smoking in the occupational setting."

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Two recent, large-scale studies in the U.S. and the U.K. compared perceptions of individual exposures to ETS (by self-report) with actual levels of ETS constituents collected in the subjects' breathing zones by personal monitors in agreement with OSHA practice.[70,83] In the U.S. study, greater than 50 percent of all self-reports of ETS exposures occurred at work. Actual exposure measurements, however, indicated that average exposure levels were approximately four to six times greater in venues outside the workplace.[83] In the U.K. study, individuals subjectively ranked relative contributions of ETS as leisure > work > home > travel.[70] Measured exposure levels, however, indicated a ranking of: home > leisure > work > travel. The authors suggest that the discrepancy between subjective rankings and objective measurements of exposure may be due to the subject's inaccurate estimate of the time spent in each venue. Other researchers have studied variations in subjective perceptions of exposure and have reported that perceptions will vary depending or whether or not the exposure source (i.e., the smoker) can be seen.[84]

5. Cotinine Measurements Do Not Validate Questionnaire Responses

Nicotine, because it is characteristic of tobacco smoke in the air, has been used extensively as an ambient air exposure marker for ETS.[15,70,83,85] Likewise, cotinine, one of the substances converted from nicotine by the body, has been used as a biomarker

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(internal dose marker) for nicotine (and ETS) exposures.[86-90] Several researchers, including Riboli, et al., of IARC, have used measurements of cotinine in an attempt to validate self-reports of ETS exposures.[87,90-92]

The advantage of body fluid measurements of cotinine over nicotine is that cotinine has a longer half-life (17 hours vs. 3 hours). Despite this longer half-life, however, cotinine-derived estimates are of little value in determining past (greater than one week) exposures to nicotine. As Reasor has written:[33]

> At present, however, there is no reliable way, through the use of biological markers, to assess long-term exposure to ETS.

Cotinine has even more fundamental problems when used as a biomarker for exposure to ETS.[81,88,93-97] For example, an individual will metabolize and clear cotinine from his/her system at different rates at different times (intra-individual variation), and clearance rates vary considerably from individual to individual (inter-individual variation).[93,95,98] Common foods also contribute trace levels of nicotine (which are thus converted to cotinine), thereby confounding inferences about ambient nicotine (ETS) exposures.[99] Moreover, body fluid levels of cotinine do not correlate well with ambient levels of nicotine (or any other constituent of ETS),[64,70,81,93,96] and saliva, plasma and urine levels of cotinine are also poorly correlated.[64,95]

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Large intra- and inter-subject variabilities in the conversion, metabolism and clearance of cotinine call into question the validity of its use in surveys that employ single-point measurements (of cotinine) to represent ETS dose.[100] Dr. Paul Nelson of R.J. Reynolds recently observed: "It is likely that inter-individual variations in nicotine and cotinine metabolism or excretion would far outweigh the small incremental increase in cotinine concentration following exposure to typical levels of ETS nicotine. In other words, the variation between people is larger than the variation due to normal exposures."[101]

Virtually every cotinine measurement survey relied upon by U.S. EPA for ETS exposure estimates was restricted to single-point measurements of cotinine.[86,87,91,92] However, an individual's cotinine level at a single point in time will be determined by the timing of the specimen collection, and by the individual's own rates of uptake, metabolism and clearance. Thus, Idle observes:[95]

> Single point cotinine concentrations can give no more than a clue of past exposure to pyridine alkaloids [such as nicotine] of unknown amounts, at an unspecified time, by an unknown route of entry and from unknown origins.

Phillips, et al., reported extremely poor correlations between salivary cotinine values and 24-hour respirable particle and nicotine exposure measurements.[79] The data from the Phillips,

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et al., study indicate that some subjects who were exposed to high levels of particles and nicotine had **no** detectable cotinine levels, while some subjects exposed to low levels of ETS, as determined by personal monitor, exhibited high levels of cotinine.

O'Connor, et al., reported levels of urinary cotinine that "did not differ" among ETS exposed and non-exposed.[81] Ogden, et al., reported "virtually identical median levels of salivary cotinine" for all subjects, even though nicotine exposures varied nearly three-fold between exposed and non-exposed individuals.[96]

Cotinine measurements likewise do not correlate well with self-reports of ETS exposures.[70,75,80,87,102,103] Wagenknecht, et al., found that 58 percent of 575 study participants who reported ETS exposures of 42 hours or more had **no** detectable serum cotinine levels; of the 186 individuals who reported no known exposures, 23 percent had a detectable cotinine level.[102] Delfino, et al., examined salivary cotinine levels and compared them with questionnaire-derived responses about ETS exposures.[103] No correlations were reported.

In 1994, Emmons, et al., reported that nearly half of those individuals who recalled exposure to ETS at work had nondetectable cotinine concentrations, as did 29 percent of those who reported exposures at home.[87] Coultas, et al., found that both

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urinary and salivary cotinine levels of workers, measured post-workshift, "varied widely with self-reported exposures."[75] Similar results were reported by Heller, et al.,[94] and Suadicani and co-workers.[104] In the latter study, investigators reported that individuals who were classified (by self-report) as "often exposed," "occasionally exposed" and "rarely/never exposed" exhibited similar average serum cotinine levels of 25, 22, and 24 ng/ml, respectively.[104] Tunstall-Pedoe and coworkers recently reported poor correlations between self-reported ETS exposure and serum cotinine level.[89] They concluded that "their poor correlation with each other . . . undermine[s] the validity of the two measures of passive smoking."

Despite acknowledged shortcomings in the use of cotinine as a quantitative biological marker for ETS, some researchers nevertheless have used cotinine measurements in an effort to validate self-reports of ETS exposure.[86,91] Riboli, et al., for example, reported that mean urinary cotinine levels among their study population showed a linear increase with self-reports of ETS exposure, and that cotinine levels were indicative of reports concerning the duration of exposure and the number of cigarettes smoked in the presence of the subject.[91]

Close examination of the Riboli, et al., study data reveals, however, that 20 percent of the study population had

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nondetectable cotinine levels, and that a predicted increase of 5 ng/ml urinary cotinine could be calculated from self-reported exposures ranging anywhere from six to 83 cigarettes per day.[31]

Riboli, et al., do not indicate the existence of any overlap in cotinine measures among the groups examined.[31] Other researchers, however, have reported wide variations of cotinine measures within specific levels of reported exposure.[63,70,87] For example, Phillips, et al., reported "considerable variation in the direct measurements [of cotinine] corresponding to the higher grades of subjective [ETS] assessment."[70]

Even proponents of the use of cotinine to validate self-reports of ETS exposures realize the limitations of the method.[63] Cummings, et al., provide the following caveats to their study:[63]

> Cotinine was chosen as a biological marker of ETS exposure because it is specific to tobacco smoke. However, cotinine levels in body fluids may not only reflect environmental exposure to tobacco smoke, but also factors that influence uptake and metabolism of nicotine.

And:

> The relatively modest correlation between reported ETS exposure and urinary cotinine indicates that other factors such as differing metabolic rates and body size may have a confounding effect on the relationship between cotinine levels and questionnaire measures of ETS exposure. In view of this finding, we

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would recommend against using cotinine levels as a strictly quantitative indicator of ETS.

6. A Potential Bias in ETS Questionnaire Data

Self- (and surrogate) reports of exposure to ETS are neither accurate nor reliable when compared to a standard of personal measures of exposure to airborne ETS constituents. Questionnaires are limited by accuracy of recall and the individual's ability to provide comprehensive, quantitative estimates of exposure over time. Other problems beset the questionnaires used in studies on ETS. As Tager notes:[105]

> Among the most significant limitations of existing questionnaire data [on ETS] are the facts that many of the questions were not designed specifically to investigate involuntary exposure, or the questionnaires have been incomplete in their probing of the circumstances of exposure (e.g. intensity, duration, specific location, etc.). These limitations have made it difficult to provide even semi-quantitative exposure estimates over time.

The accuracy of an exposure estimate is of obvious importance because of its profound effect on risk estimates in epidemiologic studies.[106] Garfinkel, et al., in a spousal smoking study published in 1985, reported different risk estimates ranging from 0.46 to 3.57 depending upon who responded to questions about exposure. If a nonsmoking wife or smoking spouse responded to the

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exposure questions, the estimated risk from spousal smoking was below unity, i.e., no increased risk. If a son or daughter responded, the estimated risk rose to over 3.00. Responses were also influenced by changing the wording of the exposure-related questions.[106]

An entire range of potential biases is introduced through the improper design and administration of specific questionnaires. One particular bias, however, is directly applicable to the ETS exposure issue. It is one that arises, in part, from the way in which ETS exposure questions are phrased and presented -- called "recall bias."[72,107-109] Recall bias in relation to ETS is a differential bias, in that cases and controls are likely to be affected differently.[72]

Given the tremendous publicity generated, for example, by the U.S. EPA's classification of ETS as a "known human" carcinogen, it is without question that a nonsmoking lung cancer case could be influenced by such publicity in the effort to account for his/her disease. If ETS is mentioned or prompted in any way by the questionnaire or interviewer, the likelihood increases that ETS will be selected by the respondent as "the correct answer."[107] A control, or someone without lung cancer, is not likely to respond in that way. Tunstall-Pedoe, et al., for example, found that self-reports of exposure exhibited strong associations with symptoms,

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while the relationships were "weak or absent" for cotinine levels.[99] The authors suggest that individuals with respiratory conditions may exaggerate ETS exposures, thereby creating a (recall) bias in self-reported exposure estimates.

The influence upon the respondent by the way a question is phrased or asked may be extensive. It reflects, in Wynder's words, a "wish bias," a "tendency on the part of the subject or the investigator to reach a desired result."[107] Wynder writes:

> Research workers, like everyone else, often develop an affection for their own hypotheses and may prefer to see them supported rather than refuted. This may lead to incomplete review of the literature in which papers failing to support the hypothesis may be ignored or more subtly, may be rejected because they are considered to be of worse quality than papers that support it. Sometimes hypotheses are based on a single piece of evidence . . . The wishes of the investigator may also enter into the collection of the data. Greater care and thoroughness may be given to collection of the data from the cases than from the controls.

The foregoing analysis demonstrates that ETS exposure and the surrogate "spousal smoking history" are not the same thing. A spouse living with a smoker may or may not be exposed at home, and he or she may or may not be exposed elsewhere. If an individual is truly exposed to ETS, the questionnaire response provides no information on the concentration or frequency of exposure. Thus,

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if meaningful at all, the surrogate "spousal smoking" may be more of a measure of the many lifestyle factors surrounding marriage to a smoker than it is of ETS exposure; indeed, a history of spousal smoking may have a number of implications for disease that have nothing whatsoever to do with exposure to ETS.[110]

E. Relevant Animal Inhalation Studies Were Essentially Overlooked in the U.S. EPA Risk Assessment

U.S. EPA's risk assessment overlooked the vast majority of relevant animal data,[1] citing only a few studies. This omission severely undermines the claim that the U.S. EPA's conclusions are based on the "weight of the evidence." As the following discussion will show, if Cal/EPA were to review all the relevant animal data, it would be clear that those data provide no support for a claim that ETS exposure is associated with lung cancer.

The data in animal inhalation studies reported to date provide no support for a claim that there is "biological plausibility" for the position that ETS exposure is causally related to lung cancer. These data are not referenced in the Excerpt.

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The "carcinogenic agents" supposedly identified in tobacco smoke (e.g., the "list" of suspected carcinogens referred to in the U.S. EPA Risk Assessment) either are not suspected **pulmonary** carcinogens or have not been unequivocally demonstrated as tumorigenic to human tissue or to the lung tissue of experimental animals.[13,111,112]

In conjunction with U.S. OSHA's lengthy rulemaking process (which is still underway), several reviewers have examined and summarized the available animal inhalation studies relevant to U.S. OSHA's claim that animal inhalation studies provided supporting data for an ETS-lung cancer relationship. These reviewers unanimously conclude that the animal studies do not support the claimed carcinogenicity of ETS.[113-117]

One reviewer, Christopher R.E. Coggins, Ph.D., concluded that animal studies using close surrogates for ETS "show no meaningful toxicological changes, even at massive exaggerations of real-world ETS concentrations."[113] Similarly, Gordon Newell, Ph.D., told U.S. OSHA that studies using a number of animal species have "failed to support the hypothesis that fresh tobacco smoke causes lung cancer" in those species.[114]

Moreover, Gio B. Gori, Sc.D., noted in his submission to U.S. OSHA's rulemaking record:[115]

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> Experimental data offer no plausible argument to classify ETS as a human risk . . . The arbitrariness of a priori assumptions of ETS-related human risks is further underscored by equivocal and uninterpretable epidemiologic reports.

Overall, tobacco smoke inhalation studies have not produced an increased incidence of lung tumors in experimental animals compared to controls; the relevance of other routes of exposure (e.g., skin painting) is questionable.[116,117] The vast majority of the available data from animal inhalation studies using surrogates for ETS deal with subchronic exposures, which are of minimal relevance to the question of the claimed "carcinogenicity" of ETS. Nevertheless, none of the subchronic studies report data supporting any permanent changes following subchronic exposure of animals to sidestream smoke at levels exceeding those encountered in "real-life" situations. Brief summaries of the subchronic studies follow.

In two 1987 papers, Haley, et al., present preliminary reports on an American Health Foundation study, in which hamsters were exposed to mainstream or sidestream smoke 7 days/week for 18 months.[118,119] Apparently, however, no final report has been published. In those reports, the authors note that smoke-exposed animals were living longer than were sham or cage control animals. No additional information was presented.

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von Meyerinck and colleagues (1989) describe a study in which rats and hamsters of both sexes were exposed to sidestream smoke at a concentration of 4 mg/m^3 TPM and 25 to 30 ppm carbon monoxide for 10 hours/day, five days/week for 90 days.[120] These authors note about their exposure system: "The levels in the exposure chamber were at least 1 and in some instances 2 orders of magnitude higher than reported for smoke-polluted rooms under real-life conditions." (Elsewhere, the authors described these conditions as "unrealistically high."[121]) One hundred animals of each species were exposed, 115 of each species were sham controls, and 100 of each species were room controls. The authors reported minor, completely reversible histopathological changes in the nasal cavity in rats only, and no alterations in any other part of the respiratory tract.

Male rats and male hamsters were nose-only exposed to fresh sidestream smoke (FSS) for seven hours/day, seven days/week for 90 days, in a study reported in 1994 by Teredesai and Pruehs.[122] One group of 20 animals was exposed to FSS with a total particulate matter (TPM) concentration of 2 ug/L, one to FSS with TPM of 6 ug/L, and one served as a sham exposure group. Histopathological changes described as "slight" were reported in the nose and larynx of exposed rats, "mainly in the high FSS concentration group." These changes were reversible following cessation of exposure. The

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authors noted that "[n]o smoke-exposure-related histopathological changes were observed in trachea and lungs."

In the subchronic study of Coggins, et al.,[123] aged and diluted sidestream smoke was used as a surrogate for ETS. This substance may be a more appropriate approximation of ETS than are other forms of tobacco smoke. Effects (hyperplasia and inflammation) were reported only in animals exposed to particle concentrations some 100 times higher than typical real-world concentrations. Coggins, et al.,[124] also report the same minor, completely reversible histopathological changes. The changes did not progress over longer periods of exposure, and once again occurred only at particle concentrations some 100-fold higher than real-world levels.

In a 14-day inhalation study, one would not expect lung tumors to develop. Thus, the relevance of the work of Coggins, et al., to the discussion of cancer is limited. Nevertheless, Coggins, et al. show only minor, reversible cellular changes following intense exposure to a surrogate for ETS.[125]

Only one animal inhalation study to date has used exposures to a surrogate for ETS of a duration sufficient for it to be considered a chronic study.[126] Witschi, et al., recently reported the results of a study, specifically designed to produce

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lung tumors in the strain of mouse used, which failed to show any significant difference between unexposed animals and animals exposed to a surrogate for ETS. The strain used lives less than one year and is known to develop lung tumors within four to six months after the beginning of exposure to various chemicals.

In the Witschi, et al., study, these mice were exposed (whole-body) to concentrations of aged sidestream smoke well in excess of measured "real-world" levels. (While not equivalent to ETS, sidestream smoke has been used as a surrogate in animal studies.) Despite the demonstrated sensitivity of this strain of mouse, the authors reported the following: "The number of animals bearing lung tumors was the same in smoke-exposed as in filtered air-exposed animals as was the average number of tumors per lung." These data are compatible with the conclusion that sidestream smoke, under the test conditions, is not a lung carcinogen in this strain.

In a recent review of the relevant literature, Rodgman cautions:[13]

> Classifying a substance as tumorigenic or 'carcinogenic' can be misleading. Often, these terms are overinterpreted. One must be aware of the precise meaning and limitations of the terms tumorigenicity and carcinogenicity when applied to specific

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compounds and must exercise considerable care in the use of these and related terms.

* * *

Many of these 43 MS and/or tobacco components [claimed to be carcinogens] should be excluded from the list on the basis of published data on their tumorigenicity (or lack of it) in laboratory animals at levels determined in MS, their lack of tumorigenicity in most instances on inhalation, and the equivocal evidence of their tumorigenicity in humans at levels in MS.

In this major review, Rodgman also writes:

[I]nhalation studies from 1936 to date involving lifetime exposure of laboratory animals to whole cigarette MS have consistently failed to induce squamous cell carcinoma . . .

The failure to produce in MS-exposed laboratory animals the tumor type reported to be associated with smoking in humans is important not only with regards to the biological properties of MS itself but also with respect to that of diluted MS delivered to the caged animals. . . .

If, as Stewart and Herrold (1962) noted, these smoke-inhalation experiments more closely resembled passive smoke (or ETS) exposure than human exposure during actual smoking, then substantial evidence is available to demonstrate that exposure to 'passive smoke' (or ETS), more concentrated than that encountered in the human situation, is ineffective in induction of the tumor type supposedly associated with cigarette smoking in humans . . .

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The above discussion illustrates that the available animal inhalation data provide no support for the claimed "biological plausibility" that ETS exposure is associated with an increased lung cancer risk. The unreferenced statement made in the Excerpt is not representative of the actual state of the scientific literature, and as such, results in a misleading impression being conveyed to readers of the Excerpt. Cal/EPA should review the relevant animal inhalation studies and the critiques/discussions already in the U.S. OSHA rulemaking record as it revises this Excerpt.

F. Data on Genotoxicity and Related Endpoints Were Essentially Overlooked in the U.S. EPA Risk Assessment

The U.S. EPA Risk Assessment fails to reference a number of actual studies comparing levels of mutagens and other genotoxic markers in the body fluids of exposed and non-exposed nonsmokers.[127-136] The results of those studies suggest no statistically significant increases in mutagenic activity in the body fluids of nonsmokers exposed to realistic levels of ETS compared with nonsmokers who are not exposed.

When considering data on genotoxicity, it is important to put the genetic changes reported in such studies into context. All forms of life are constantly exposed to physical and chemical

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agents in the environment (e.g., radiation) and to endogenous (internal) agents with the ability to cause changes in DNA. According to Bruce Ames, developer of the Ames assay for mutagenicity, human exposure to potentially mutagenic or carcinogenic substances is much greater than generally appreciated, i.e., the environment can be thought of as "filled with potential carcinogens."[137] DNA has been called an "unstable" molecule, and it has been noted that **endogenous** DNA damage may occur at the rate of 100,000 base pairs **per cell, per day**.[137,138] Thus, DNA is **not** completely stable; changes are regularly occurring, but for the most part, do not result in heritable effects on the organism. As toxicologist Christopher R.E. Coggins of R.J. Reynolds stated in testimony before U.S. OSHA, "Toxicologically, I'm not sure that we really know what mutagenesis really means because of . . . DNA repair."[139]

Therefore, conclusions about genotoxicity obtained from in vitro systems, while certainly providing some information about the substance being tested, must nevertheless be put into the proper biological context. The magnitude of a genotoxic response in the whole organism may be substantially different than that observed in a bioassay.[140,141] As Ames and Gold noted:[140]

> [H]umans have numerous inducible defense systems against mutagenic carcinogens, such as DNA repair, antioxidant defenses, glutathione

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> transferases, and so forth . . . [L]ow doses of carcinogens appear to be both much more common and less hazardous than is generally thought.

The difficulty of extrapolating from in vitro genotoxicity to in vivo carcinogenicity is illustrated by data presented in the recent animal inhalation study of Witschi, et al., which used sidestream smoke.[126] Other studies suggest that tobacco smoke condensates may be mutagenic when tested using in vitro systems; however, there are no such studies using ETS condensates. In their recently published chronic inhalation study, Witschi and colleagues reported no differences in the total number of animals with tumors or in the average number of tumors per lung in the smoke-exposed animals when compared to filtered air-exposed control animals -- consistent with sidestream smoke **not** being carcinogenic under the test conditions -- even though they did report positive results for molecular biomarkers. Thus, these data suggest that the relationship of mutagenicity to "carcinogenicity" is not clear-cut.

In another study, Nikula, et al. (1995), investigated the inhalation carcinogenicity of two substances that were essentially equivalent, except that one contained mutagens and the other did not.[142] If mutagenic properties were relevant to carcinogenicity, it would be expected that the substance with mutagens would have

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produced a stronger carcinogenic response. However, as the authors noted, the two substances yielded "very similar" responses in the test system. Thus, these data, too, suggest that positive genotoxicity results cannot necessarily be correlated with carcinogenicity.

In its Proposed Rule, U.S. OSHA discussed a number of studies in which cigarette smoke or cigarette smoke condensate was tested in the Ames Salmonella typhimurium assay, and an increased mutation rate was reported. OSHA's inclusion of studies dealing with mainstream and sidestream smoke revealed the misconception pervading the Proposed Rule that ETS, mainstream, and sidestream smoke are equivalent.

Moreover, OSHA omitted at least one relevant study from this discussion in the Proposed Rule. In 1991, Bombick, et al., reported on a cellular smoke exposure technique using rat liver cells and the Ames Salmonella assay.[135] After a three-hour exposure using ETS at a concentration of 1.5 mg total particulate matter/m^3, the authors report:

> Using the neutral red cytotoxicity and Ames mutagenesis assays there were no differences observed in the ETS-exposed cells and their respective room air controls, indicating that ETS was **biologically inactive as tested**. (emphasis added)

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Studies have reported that various constituents and extracts of ETS collected from indoor air are capable of inducing mutations in the Ames assay.[143-149] However, the significance of such reported findings has not been established. Virtually all air samples, whether in the presence or absence of smoking, can be shown to be mutagenic in various bioassays. Indeed, many substances, including foods and other "natural" materials, have been shown to exhibit mutagenic and/or carcinogenic properties.[148]

Of relevance, Sonnenfeld and Wilson report that sidestream smoke exhibits reduced activity as it ages and becomes diluted, that is, as it becomes ETS.[149] These authors report on an experiment in which cultured mouse fibroblast-like cells were exposed to mainstream or sidestream smoke of various ages. In this report, cytotoxicity (cell mortality) is used as a measurement of DNA damage sufficient to cause cell death. The authors write:

> Aging of SS smoke resulted in a rapid decline in the mortality generated by the smoke. As calculated from the linear regression curve, an increase in age of SS smoke of 30 [seconds] after generation would have resulted in a **total** loss of cytotoxic effects. (emphasis added)

Another area of relevant research comprises those studies that have compared the mutagenicity of body fluids of nonsmokers exposed to ETS and nonsmokers not exposed to ETS. Several of these

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studies report no significant difference in mutagenic activity.[129,130,134,136,150,151]

For instance, in a study by a team of German researchers, ten nonsmokers were exposed to ETS, generated by human smokers, for eight hours under two exposure conditions.[138] The two experiments were characterized by CO levels of 10 ppm and 25 ppm, respectively; according to the authors, both exposure regimes represent higher exposures than "real-life" situations. Elsewhere, they describe Experiment 2 as "far from being realistic,"[134] and bearing "no relation to a real-life situation."[136] In addition, the authors controlled for the effect of mutagens from the diet by keeping their subjects on a diet low in polycyclic aromatic hydrocarbons. Urine samples from both smokers and nonsmokers were tested in the Ames Salmonella assay. The authors report:[130]

> All urine extracts of ETS exposed non-smokers were found to be negative in the mutagenicity test when applying the [criterion] of Ames (doubling of spontaneous mutation rate).

Thus, even at exposure levels higher than would be expected on average, no increase in mutagenicity could be measured. These data do not support claims that ETS exposure is associated with an increase in mutagenic activity; moreover, because the samples come from exposed humans, the influence of physiological processes following exposure is indirectly taken into account.

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Citing the high variability of measures of urinary mutagenicity and questions about the relevance of increased urinary mutagenicity to cancer risk, the authors write:[136]

> The data suggest that nonsmokers in real-life situations take up very low doses of ETS constituents, and detoxification of the genotoxic substances inhaled is effective.

And:[137]

> Whether ETS exposure can lead to an elevated urinary mutagenicity is a matter of controversy. In most investigations no significant increase has been observed. . . .
>
> . . . The results of our investigations, as well as those of other authors, suggest that urinary mutagenicity, which would be a potential marker for ETS particle exposure, remains unchanged after ETS exposure.

The few studies reporting statistically significant increases in urinary mutagenicity among individuals exposed to ETS do not employ realistic levels of exposure to ETS, nor do they control adequately for the presence of mutagens in the diet of the study subjects.[152-154] For instance, in the Bos, et al., study, the exposure condition consisted of the smoking of 157 cigarettes over six hours in a room with "poor ventilation."[152] The relevance of such an exposure to "real-life" conditions is certainly

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questionable. With respect to diet, Bartsch, et al., acknowledge, concerning their study, that[154]

> Urinary mutagenicity is influenced also by dietary habits; although we collected information on diet, the dimension of the study (particularly as far as passive smokers are concerned) does not allow adequate statistical treatment of this potential confounding factor.

Other related studies have examined levels of various DNA changes in nonsmokers exposed to ETS.[131,138,151,155-158] Based on the data presented in these studies, nonsmokers exposed to ETS do not appear to exhibit increased DNA adduct formation, nor do studies report increased levels of chromosomal changes in cells of nonsmokers exposed to ETS. Discussion of these studies follows.

Collman, et al., collected data from 16 nonsmokers, 15 "passive smokers" (currently living with one or more smokers), and 13 current smokers, all women.[156] Sister-chromatid exchange (SCE) frequencies in lymphocytes (a type of white blood cell) were compared with and without coincubation with a chemical that enhanced the frequency of SCEs. Based on both assays, the authors report that "the frequency of SCEs in persons passively exposed to smoke was not higher than in nonsmokers."

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In a report by Husgafvel-Pursiainen, peripheral blood lymphocytes were examined for SCE frequency, a sensitive test.[157] This test uses cells **from the exposed individual**, rather than another organism, and also considers repair mechanisms, thus being a better representation of actual events at the cellular level. Study groups consisted of 12 smoking waiters and waitresses, 20 nonsmoking waiters and waitresses who were occupationally exposed to ETS, and 14 nonexposed office workers. The author reports that "[t]he mean SCE level in exposed non-smokers did not differ from that observed in the non-exposed group." Although no ETS measurements from the restaurants were reported, the author characterizes them as "heavily polluted," and the exposure as "long-term." This study, which reports data from persons exposed in a "real-life" situation, does not support claims of the genotoxicity of ETS.

Chromosomal aberrations (CAs) and SCEs were examined in peripheral blood lymphocytes from nine smoking waiters, 16 nonsmoking waiters exposed to ETS at work, and seven reportedly nonexposed nonsmokers by Sorsa, et al.[155] The authors report that "[n]o significant differences were seen between the groups or subgroups in the 2 parameters." Thus, no "genotoxic" effects could be detected in persons exposed to ETS at "real-world" occupational exposures.

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Holz, et al., report that DNA adduct levels were compared in monocytes (a type of white blood cell) of smokers and "heavily exposed passive smokers," who had been exposed in a chamber.[131] DNA adducts above background were reported in smokers; they disappeared in less than 40 hours. The authors report no above-background adduct levels in study subjects exposed to ETS.

In a study by Gorgels, et al., 50 self-reported ETS-exposed men ("passive smokers"; average 72.8 hours exposure per week) were compared with 56 self-reported low ETS-exposed men (average 5.1 hours per week).[158] SCEs in cultured lymphocytes were examined; the authors report that "[n]o difference was observed between low exposed non-smokers and the passive smokers." They conclude:

> Our results are in accordance with previous smaller studies in less homogeneous populations of non-smokers. These studies also failed to demonstrate even a tendency for an association between passive smoking and SCE levels.

Five male smokers, five male nonsmokers, and five male nonexposed nonsmokers were compared in Holz and colleagues' 1993 paper.[130] The endpoint examined was DNA single-strand breaks (SSBs), "considered to be an important parameter of genotoxic stress," in lymphocytes. The authors write:

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> All probands revealed measurable and varying SSB levels. Since DNA is an unstable molecule and estimated endogenous damage exceeds 100000 affected base pairs per cell per day, we assume that SSB base levels reflect unrepaired lesions. Active smoking caused an increase in SSBs in peripheral blood lymphocytes. This effect could not be found in passive smokers.

ETS exposure in this study consisted of five smokers each smoking 24 cigarettes in eight hours in an exposure chamber. This study provides no support for claimed genotoxic effects of ETS, even at a high exposure level.

This review of data from studies in which genotoxicity was assessed in persons actually exposed to ETS thus provides little, if any, support for the contention that ETS is genotoxic at levels encountered in workplaces and other indoor environments. As Doolittle stated in his submission to U.S. OSHA:[159]

> The hypothesis that ETS causes lung cancer is not supported by any of the available genotoxicity data. There is no evidence that ETS at or near ambient levels of exposure produces genotoxicity. The available published evidence comes to the opposite conclusion, namely ETS is not genotoxic.

G. Conclusion

In conclusion, the U.S. EPA Risk Assessment on ETS is not the definitive document portrayed by Cal/EPA. A large number of

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unresolved questions and uncertainties remain. Moreover, more recent data on exposure, animal inhalation studies and genotoxicity do not conclusively support U.S. EPA's conclusions, contrary to the statements made by Cal/EPA.

A large number of the submissions and articles critical of U.S. EPA's risk assessment are now part of the U.S. OSHA rulemaking record. U.S. OSHA also relied heavily on the U.S. EPA Risk Assessment, and commenters have called upon OSHA to critically evaluate its conclusions.

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SECTION IV: CAL/EPA'S TREATMENT OF THE EPIDEMIOLOGIC DATA OVERLOOKS A NUMBER OF IMPORTANT ISSUES

The following discussion will address a number of problems with Cal/EPA's treatment of the epidemiologic literature on ETS exposures and lung cancer in the Excerpt. A selection of relevant references is submitted as Appendix II.

A. Cal/EPA Fails to Acknowledge the Magnitude of the Limitations of Weak Association Epidemiology

Members of the scientific community have criticized the epidemiologic studies on ETS exposure and lung cancer for failing to consider certain factors, namely bias and confounding, that could affect the validity of the studies' risk estimates. The impact of such factors is particularly important in studies that, like these studies, report risk estimates that are "weak."[1,2] A weak association is represented by a risk estimate of less than 2.0 or perhaps even less than 3.0.[3-6] As Wynder notes:[3]

> [E]pidemiology has problems when the associations are of a low order of magnitude. In such instances, findings in the literature are, in general, inconsistent. . . .
>
> When risks are small, and especially when effects occur many years after their causes, detecting them, estimating their magnitude, and assessing their importance for the community in light of other relevant factors pose problems of study design, data collection, analysis, and interpretation which can be exceedingly difficult. (p. 139)

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Specifically, Gori (1995) comments about the ETS epidemiology:[7]

> The weak data on ETS are compatible with either a slight increase or a decrease of risk, but are impotent to certify either conclusion on a scientific basis. In the unlikely hypothesis that ETS were a risk, it would have to be small beyond detection because of the **inevitable and excessive noise to signal ratios of its epidemiology.** (p. 20) (emphasis added)

1. Cal/EPA's Discussion of the Potential Impact of Confounders in the Spousal Smoking Studies Is Incomplete

In the Excerpt, Cal/EPA essentially dismisses the possibility that confounding factors could contribute to the increased lung cancer risk reported in some of the spousal smoking studies. (p. 22) Cal/EPA cites only a few studies other than some of the spousal smoking studies themselves, in a review that is clearly incomplete and selective.

The use of spousal smoking status as a proxy for ETS exposure introduces substantial uncertainties into estimates of risk. Spousal smoking (marriage to a smoker) does not measure ETS exposure alone, but rather encompasses numerous variables that may be related to lung cancer risk.[8-12] These other variables, or

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confounding factors, are factors associated with the exposure being studied (here, spousal smoking status) **and** with an increased risk of the outcome under consideration (in these studies, lung cancer). Confounders may seriously affect estimations of risk purportedly due to ETS exposure.

As noted in a recent review:[13]

> Because the relative risks or odds ratios for human diseases reported to be associated with ETS exposure are typically no larger than the risks for confounding lifestyle factors, epidemiological studies of the association between ETS exposure and chronic disease should be designed to maximize data quality and statistical power.
>
> The ETS and chronic disease epidemiology studies conducted to date have not adequately controlled for all of the known confounding variables.

Few of the spousal smoking studies upon which Cal/EPA relies have taken even some of the many potential confounding factors into account. Therefore, the possible impact of confounders on risk estimates attributed to ETS is of paramount importance. Since actual ETS exposures are not measured in these studies, where reported spousal smoking status is used as a surrogate for ETS exposure, the risk estimates claimed for ETS are instead risk estimates for "marriage to a smoker." A number of

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potential lung cancer risk factors are associated with household smoking status.[14,15]

One of the most important potential confounders of the claimed ETS-lung cancer relationship is dietary differences between "smoking" and "nonsmoking" households. [A "smoking" household is one in which at least one person smokes; a "nonsmoking" household contains no smokers.] In epidemiologic studies, when a nonsmoking case or control reports marriage to a smoker, this would correspond to living in a smoking household.

Diet appears to be a true confounder of the spousal smoking-lung cancer relationship.[16,17] Diet satisfies the first necessary condition for being a confounder by being associated with lung cancer risk, as has been shown in a number of studies.[18,19] Second, dietary differences are associated with household smoking status; that is, the diets of nonsmokers living with smokers differ from the diets of nonsmokers living with nonsmokers.

Data show that smokers' diets are generally different from nonsmokers' diets.[20-28] In particular, the data, already suggestive of differences in diet according to household smoking status, have been dramatically strengthened by the addition of several recent studies.[8,29-32] Taken as a whole, the data strongly support an association between household smoking status and diet.

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Since diet is associated with lung cancer risk, it could well be a confounder in the spousal smoking studies which have failed to adequately account for diet in their analyses. The magnitude of the risks reported for some dietary exposures suggests that if only a few cases in a study had such exposures, it could have a significant impact on the risk estimates attributed to ETS exposure.

The following are brief comments on some of the recent literature that illustrates the correlation between diet and other lifestyle factors and household smoking status.

- A 1992 British study examined the consumption of fried foods, fats, fruits, vegetables, and sweets in smokers, nonsmokers, and exsmokers.[22] The authors reported that nonsmokers who live in smoking households "have a diet more like smokers," and that "diet could be an important confound in epidemiological studies of ETS." The authors also noted:

> Our analysis showed that non-smokers in smoking households ate fried food more often, more chips [french fries], less fruit in winter, more butter and less margarine high in polyunsaturates than non-smokers in non-smoking households. As we have pointed out, these habits are thought to increase the probability of cancer.
>
> These results suggest that it is wise to show caution when interpreting the disease patterns

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> of non-smokers in smoking households. Studies to date have failed to take into account the effect that differences in dietary and lifestyle behaviour between 'smoking' households and 'non-smoking' households may have on the incidence of cancer or heart disease.

In a 1993 paper, the same authors reported that, in addition to having higher intakes of saturated fats, never smokers living in smoking households consumed fats more often, drank more alcohol, and ate fewer root vegetables and cereal than did never smokers living in nonsmoking households.[23]

- Thornton, et al. (1994), examined 33 lifestyle factors in a survey of 9,003 British adults.[9] They report:

> [L]ike current smokers, passive smokers tended to be less educated; of lower social class; work in 'risky' occupations; drink more alcohol; do nothing to keep healthy; take longer before their first meal of the day; eat more fried foods and bread; eat less cereal, fruits, salads and low fat/polyunsaturated spread; drink more tea (but not more coffee); use more sugar in tea and coffee; not cut down on fatty foods; and be more neurotic and extrovert.

Thornton, et al., summarize their study as follows: "It has not perhaps been documented clearly before that smokers and non-smokers differ in so many lifestyle characteristics and that these are **nearly always in the direction of predicting a**

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higher risk of disease." (emphasis added) The authors also point out the importance of considering these factors, particularly when investigating weak associations in epidemiology, such as those claimed for ETS.

- Matanoski, et al. 1995[39], report on analyses of data from the NHANES I study, comparing nutritional and behavioral characteristics between nonsmoking women whose husbands smoked and nonsmoking women whose husbands were nonsmokers.[39] Nonsmoking women with smoking spouses were statistically significantly more likely to have an urban residence, to consume beef and the skin on poultry (both suggestive of increased fat intake), to drink alcohol, and to consume less of certain vitamins and other nutrients than did nonsmoking women married to nonsmokers. The authors summarize the importance of their findings as follows:

> [E]xposure to household tobacco smoke may not represent just a single exposure but a complex of factors, many of which, such as low vitamin intake and high alcohol intake, have been shown to influence the risk of cancer.

While the Matanoski, et al., study is referenced in the Cal/EPA Excerpt, the treatment is superficial and does not give adequate attention to the importance of this study's findings.

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- Emmons and colleagues (1995) also compared the diets of persons living with smokers and living with nonsmokers.[9] Their data further support the differences between smoking and nonsmoking households: persons living with smokers had less healthy diets overall, consuming more fat and less fiber, fewer fruits and vegetables, and fewer micronutrients than did nonsmokers who lived with nonsmokers. All the reported differences were statistically significant.

The importance of the potential impact of dietary confounding on reported estimates of lung cancer risk from the spousal smoking studies was described by Layard in a submission to U.S. OSHA's rulemaking record.[10]

> Dietary confounding alone could easily be large enough to explain the summary U.S. spousal smoking-lung cancer relative risk of 1.09 from [Layard's] meta-analysis of female studies.

Other data suggest the importance of numerous factors associated with cancer risk that may affect the reported results of the spousal smoking studies. Few, if any, of these risk factors have been considered in the epidemiologic studies on lung cancer, nor has U.S. EPA or Cal/EPA convincingly shown that these other confounders or independent risk factors for lung cancer may be discounted. These potential confounders or risk factors would not

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have to apply to all the spousal smoking studies; if they influenced only a few of the studies, U.S. EPA's and Cal/EPA's position would be seriously affected.

For instance, recent publications have reported the following lung cancer risk factors: body weight,[13] history of radiation therapy,[14] occupation,[15] previous lung disease[16] and family history of lung cancer.[17] Moreover, in some cases, the risks reported for these other factors are far in excess of the risk estimates suggested for spousal smoking.[18]

As pointed out in the Report of the Independent Working Group to the Health Care Committee of the Australian National Health & Medical Research Council (NH&MRC), while it is difficult for epidemiologic methods to detect very low relative risks, it is conceivable that factors having low relative risks could still impact the outcome of a study.[18] The Report notes:

> [T]hree factors, each having a relative risk of 1.1, if present together would induce (assuming no interaction positively or negatively between them) an observed relative risk of 1.33. It is impossible that confounding risk factors of this magnitude would be detected in the studies we have examined. Hence although these risk factors would not be detected, they could, in aggregate, produce a relative risk at least as large as that observed for exposure to ETS.

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Similarly, a 1992 review also addressed the possibility that confounding factors may have a combined effect on estimations of lung cancer risk:[26]

> In the absence of calculations of lung cancer risk when multiple factors apply, one can only speculate on the combined effect on an individual who, for example, might have a family history of lung cancer (RR = 2-4), lived in an urban area (RR = 1.2-2.8), worked in an occupation associated with elevated lung cancer risk (RR = 2 or more), was among the physically less active groups of the population (RR = 2) and, if a female, had the risk associated with a short menstrual cycle (RR = 2.2).

Until epidemiologic studies fully account for the possible impact of confounders and independent risk factors on estimates of lung cancer risk for spousal smoking, those risk estimates must be viewed with caution and carefully interpreted. **There is no indication in the Excerpt that Cal/EPA has done this.** As Gio Batta Gori, Sc.D., writes in a comment in the U.S. OSHA public record:[11]

> [A]ttributions of epidemiologic risk to ETS cannot be rationally sustained unless confounders and biases have been convincingly controlled, and adjustments have been objectively justified.

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2. Cal/EPA Has Inappropriately Dismissed the Potential Impact of Several Sources of Bias in the Spousal Smoking Studies

When interpreting the results of epidemiologic studies, the potential effects of biases must be considered. Bias refers to factors in the design, conduct, analysis, or interpretation of an epidemiologic study that erroneously lead to the appearance of a stronger or weaker association than in fact exists. Bias (and confounding) becomes particularly important when dealing with weak associations, i.e., risk estimates of 3.0 or less.[3-6,9]

One important type of bias particular to the spousal smoking studies is smoking status misclassification bias.[10,19] Smoking status misclassification occurs when smokers erroneously report themselves as nonsmokers in response to study questionnaires. None of the spousal smoking studies to date has been able to discount smoking status misclassification as a potential source of bias.[10]

It has been implied that the Fontham, et al., study[11] is superior to the other spousal smoking studies because it had accounted for smoking status misclassification. This is an incorrect portrayal. While Fontham and colleagues did the best they could to exclude current active smokers from among cases and controls, based on cotinine measurements, cotinine does not allow

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the determination of past smoking status.[42] Moreover, Fontham, et al., measured cotinine in hospitalized cases. The vast majority of hospitals severely restrict smoking in fact, accreditation requires that smoking be banned); moreover, many lung cancer patients who happen to be smokers stop smoking after diagnosis. Thus, the cotinine measurements in this study did not even give a good indication of present smoking status, let alone previous long-term smoking status. The smoking status misclassification rates portrayed by Fontham, et al., as accurate are, in reality, not representative of the true situation.[42]

Smoking status misclassification could have a dramatic impact on the reported risk estimates in the Fontham, et al., study, and in other spousal smoking studies. For instance, a recent Congressional Research Service (CRS) Report on ETS calculated that, in the Fontham, et al.,[11] and Brownson, et al.,[43] studies, smoking status misclassification rates of **less than 10 percent** alone would account for **all** the reported elevation in risk at the highest exposure levels, and that misclassification rates of **less than three percent** would mean that those risk estimates would not achieve statistical significance at the 95 percent level.[44] Such misclassification rates are certainly possible, according to a recent review of the literature on this subject.[45]

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In addition to smoking status misclassification, another potentially important source of bias in the epidemiologic studies on ETS is misclassification of disease status, i.e., diagnosis of lung cancer. In many of the spousal smoking studies, disease diagnosis is haphazard and incomplete. Even in some of the better-designed studies, the possibility that tumors appearing in the lung may have metastasized from other sites remains likely. None of the studies confirmed lung tumor diagnosis via autopsy.

In a recent study, Kaye, et al., reported that in "emotionally charged situations," misclassification of disease diagnosis could inflate cancer risk estimates by some 30 percent.[45] Self-reports of cancer were compared with medical diagnoses of cancer for two groups of people. One group lived in a community with a hazardous waste treatment facility (test population); the other (control population) did not. The risk estimate for malignant tumors for the test population **decreased by 31 percent** when the more precise medical diagnoses were used instead of self-reports of having had cancer. The authors conclude:

> This study demonstrates the importance of verifying reported cases of disease, even a disease as well defined as cancer, in emotionally charged situations such as living in communities surrounding hazardous waste sites. If reported cases of cancer had not been verified, it would have incorrectly

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> appeared that community A had almost twice the rate of cancer as community B and that an association existed between living in community A and having cancer.

Given the increasing public attention paid to ETS, and the claims that ETS exposure is causally associated with lung cancer, ETS could be considered an "emotionally charged" issue. While this might not affect the earlier studies on ETS, it is certainly of potential importance for studies conducted in the last few years.

B. A Number of Unresolved Questions Exist Concerning the Fontham, et al., Study, Rendering Its Interpretation Less Clear than Cal/EPA Portrays

Cal/EPA offers essentially no critical comment on the Fontham, et al., (1994) spousal smoking study.[11] In fact, Cal/EPA appears to favor this study, commenting that its reported results are "closest to" those reported by the U.S. EPA in its Risk Assessment on ETS. (p. 7, 19) Moreover, Cal/EPA claims that this study "successfully addressed" the many weaknesses inherent in the spousal smoking study design. (p. 27)

Despite the contentions to the contrary in the Cal/EPA Excerpt, the Fontham, et al., (1994) study is still subject to the same limitations as the other spousal smoking studies. A number of criticisms of the Fontham study have been submitted to the public record at U.S. OSHA.[12,46,47] For instance, Sears and Steichen listed

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nine major categories of problems with the Fontham, et al., study, which they characterized as "significant design and execution flaws."[14] These included:

> [T]he study population has no male representation and is not even representative of the nonsmoking U.S. female population, under-representing rural subjects and massively over-representing minorities (especially Asians);
>
> [T]he percentage of adenocarcinoma is unusually high, possibly a reflection of abnormal demographics in the study population;
>
> [T]he phenomenon that urinary cotinine analyses fail to detect active smoking cases only, suggests that misclassification is more prevalent among the lung cancer cases than among the controls, leading to an inflated relative risk point estimate;
>
> [T]he failure to promulgate the use of colon-cancer controls to account for recall bias results in over-estimation of risk;
>
> [T]he use of frequency-only matching within age categories, combined with the high sensitivity of cancer incidence to age differences, likely introduces a bias resulting in inflated estimates of risk;
>
> [T]he categorization of individuals by broad race groupings fails too account for important lifestyle differences, especially among the large Asian subset of this study;
>
> [T]he inability of the standard linear logistic regression approach to fully account for strongly-coupled confounding variables . . . results in inaccurate estimation of risk;
>
> [T]he non-independence of the spousal-, workplace- and social-exposure study subpopulations forces Fontham's workplace

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> relative risk estimate to include potential contributive effects (including confounding) from both spousal and social exposure.
>
> [T]he absence of dose from the 'risk equation' necessitates reliance upon the recall of exposures that may have taken place decades earlier, often by a surrogate respondent.

Moreover, recent publications have raised additional questions about the Fontham, et al., study.[35,48,49] Perhaps the most serious questions about the study are raised in a post-hearing brief submitted to the U.S. OSHA record that points out what appears to be a significant misinterpretation.[49] In that submission, William Butler focuses on the data in the Fontham, et al., study concerning women who reported both childhood and adult ETS exposure. Fontham, et al., originally presented risk estimates for adult ETS exposure regardless of childhood ETS exposure status.

Butler divided the study subjects into four categories: (i) neither childhood nor adult ETS exposure (the reference group); (ii) childhood but not adult exposure; (iii) adult but not childhood exposure; and (iv) both childhood and adult exposure. He calculated a statistically significantly **negative** lung cancer risk for women with childhood but not adult exposure (OR = 0.35, 95% CI 0.12-0.99), which, he proposes, is a result of some bias in study design or data collection. Butler states that "Fontham et al.'s

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failure to mention this fact makes their analysis incomplete and their interpretation misleading."

Fontham, et al., included cases and controls from the group with the decreased risk in the comparison group for their analysis of adult lung cancer risk. According to Butler, the underlying bias became a "source of artificially inflated statistical estimates that incorrectly indicate a positive association between adult ETS exposure and lung cancer."

According to Butler, Fontham, et al., appeared to recognize that there was an "interaction" between childhood and adult exposure in the 1994 paper, but did not mention the bias identified in his reanalysis. He states that adjustment for the bias would be "expected to reduce" the risk estimates for spousal, household, workplace, and social ETS exposures. Butler then notes that Fontham, et al., have not provided sufficient data in their publications for these adjustments to be made, and suggests that the raw data from the study would be needed and should be released.

A number of other issues have been raised concerning this study. For instance, as noted earlier, despite the Fontham, et al., study's use of cotinine to assess current tobacco use, the authors themselves acknowledge that misclassification of ever smokers as lifetime never smokers is "problematic" because there is

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"no biomarker of lifetime tobacco use."[40] Moreover, only slightly more than half (54%) of cases had cotinine determinations, so that even recent active smoking was not excluded for nearly half of the cases.[41]

While the Cal/EPA Excerpt repeatedly stresses that the Fontham, et al., study is a **multicenter** case-control study, if the characteristics of the study population are examined, it is seen that the vast majority -- 81 percent and 86 percent, respectively -- of cases and controls come from two areas in California (Los Angeles and the San Francisco Bay area). Given this breakdown, the "multicenter" label is fairly misleading. Moreover, the authors provide no breakdown of the data by study center, and it is not possible to ascertain whether the reported risks were consistent across the centers. Heterogeneity in the data among study sites would argue against combining the data as was done by Fontham, et al.

Although Fontham, et al., state that "dietary cholesterol" was considered as a potential confounder, they do not provide sufficient information in the study publication describing this factor. Apparently, Fontham, et al., did not consider dietary saturated fat intake, recently reported by Alavanja, et al., to be associated with relative risks as high as 6.0 to 11.0.[42] The risk estimate was highest for nonsmoking women with **adenocarcinoma**; over

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75% of the cases in the Fontham, et al., study were adenocarcinomas. Alcohol consumption, another potential confounder, was also not mentioned. Recent studies have reported that smokers, and the persons living in their households, are likely to consume more fatty foods and more alcohol.[39]

The "adjustment" of the reported risk estimates is difficult to interpret, as the adjustment takes into account both study design variables (e.g., subject age) and potential confounders. For instance, the workplace risk estimate in the final report of the Fontham, et al., study was 1.12 before "adjustment" for several factors.[41] The "crude" risk estimate was not statistically significant. After adjustment, however, Fontham, et al., reported a statistically significant workplace risk estimate of 1.39. As was pointed out in submissions to the U.S. OSHA rulemaking record, the direction of the change was opposite what would be expected, and of a magnitude greater than many of the other adjustments in the paper.[12,46] Fontham, et al., do not provide adequate discussion of this unexpected outcome of adjustment, e.g., they do not explain which factor(s) had the most impact.

The above discussion illustrates that there are many unresolved issues concerning the Fontham, et al., study. For the Cal/EPA Excerpt to accurately reflect the nature of the ETS

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epidemiology, it should review the criticisms that have been raised concerning the Fontham, et al., study, and address them.

C. The Argument that a Number of the Spousal Smoking Studies Demonstrate a "Dose-Response" Relationship Is Scientifically Flawed and Cannot Be Used to Support Cal/EPA's Conclusions

In the Excerpt, Cal/EPA refers to reportedly increased risks in the "high exposure" subgroups from some of the spousal smoking studies and to claimed positive trends in risk estimates. (e.g., p. 19, p. 26) By so doing, Cal/EPA invokes the argument that these studies exhibit a "dose-response."

The "dose-response" argument is based on the claim that positive results of statistical tests for trend on epidemiologic data show that lung cancer risk increases with increasing reported exposure; that is, that those tests demonstrate that a "dose-response" has occurred. Those who adopt this argument further suggest that positive tests for trend satisfy the criterion for dose-response used in evaluating a causal relationship in epidemiology. As will be shown below, however, such claims about "dose-response" based on the epidemiologic studies do not withstand critical scientific scrutiny.

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1. **The ETS Epidemiologic Studies Contain No Actual Exposure Data; The Purported "Dose" Levels Cannot Be Assumed to Represent Dose at All**

The ETS epidemiologic studies do not measure actual exposures to ETS in the home or workplace. Rather, the studies rely on imprecise estimates based on individual recall. Other recent studies clearly illustrate that questionnaire responses are not accurate representations of actual ETS exposures, and are subject to bias.[30-32] As Wynder and Hoffmann[33] note:

> [I]n all ETS-lung cancer studies in 'never-smokers,' assessment of their lifetime exposure remains problematic as long as reliable biomarkers of uptake are lacking.
>
> Perhaps the greatest uncertainty about the epidemiological data is due to the unreliable information obtained by questioning volunteers in regard to their smoking habits.

H. Daniel Roth, Ph.D., noted in his submission to U.S. OSHA: "The ETS exposure data in the overwhelming majority of studies are far too weak for drawing epidemiological conclusions."[34] If the data are weak in terms of ETS exposure as a whole, they are likely even more limited when dealing with reported "specifics," such as levels of perceived exposure including the number of cigarettes smoked per day or the duration of a smoking history).

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An examination of the ETS-lung cancer epidemiologic studies reveals that they use a variety of definitions to "quantify" spousal smoking. For instance, some use number of cigarettes smoked per day without consideration of duration, while others use duration regardless of amount smoked. In addition, the studies do not use the same intervals to categorize amount smoked, e.g., the "highest exposure" in one study may be >20 cigarettes per day, while in another study, it might be >40 cigarettes per day. Thus, the highest exposure category in the first would be an intermediate category in the second. As noted in the 1995 CRS Report:[14]

> One implication of the potential disparity between the different types of exposure measurements is that combining risk [estimates from] several studies at the highest exposure levels probably yields misleading results. p. 31)

The authors of the CRS Report note elsewhere that U.S. EPA calculated just such an overall risk estimate for the highest exposure levels in the spousal smoking studies.

Given the limitations inherent in exposure estimates based on personal recall and recall by surrogate respondents, claims that the "exposure level" data in the ETS epidemiologic studies can be used to illustrate dose-response are based on a weak and inadequate foundation. Uncertainty exists with respect to both

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the actual exposures encountered by study participants and the degree to which study subjects may be misclassified according to exposure. These limitations alone suggest that it would be prudent to exercise great caution in making interpretations about "dose-response" from these data.

2. Claims that the Spousal Smoking Studies Exhibit Dose-Response Relationships Are Most Commonly Based on the Results of Statistical Tests for Trend; Such Tests Are Clearly Not Tests for Dose-Response and Should Not Be Interpreted as Such

Epidemiologists frequently imply that the results of a statistical test for trend (e.g., the Mantel extension test) provide evidence of a dose-response relationship. According to Maclure and Greenland, this overstates the evidence for dose-response, particularly if "dose-response" is considered to be a monotonic relationship, that is, one in which risk increases with each increment of exposure.[5] In fact, Maclure and Greenland point out:

> Tests for overall trend, such as the Mantel extension test, are **widely but erroneously** believed to be tests of the hypothesis that a monotonic dose-response relation exists -- that is, a relation in which risk continues to increase with each increment of exposure. (emphasis added)

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Statistical assessments of "trend" are not equivalent to developing a dose-response relationship.[18]

Maclure and Greenland point out several major statistical problems with applying the Mantel extension test to questions of dose-response.[35] First, they demonstrate mathematically that when there are few subjects in one of the exposure categories, the Mantel extension test is essentially algebraically identical to a test for overall association (the Mantel-Haenszel test). They explain the interpretation error that can arise from this misconception as follows:

> Numerous articles can be found in which authors conclude that the extension test for trend in risk over a trichotomous exposure, **when there are few subjects in one of the exposure categories**, is telling something extra. In fact, it is little more than a restatement of the results of the Mantel-Haenszel test of the collapsed dichotomous table. (emphasis added)

That is, mathematical considerations dictate that, if the subdivisions ("exposure categories") include one or more with few subjects, the Mantel extension test will have a positive result in a study reporting an increased risk when only two categories are considered. This is frequently interpreted as evidence of dose-response, when it is essentially only an artifact of the mathematics involved. The issue is relevant because a number of

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the spousal smoking studies have at least one category with less than 20 cases. Peter Lee has noted that dose-response relationships are frequently reported by those studies that report an association in the first place, an observation that would follow from the mathematical considerations described above.[32]

Moreover, Maclure and Greenland also note another limitation of the Mantel extension test: that it "**assumes** a particular dose-response model as part of its justification."[33] (authors' emphasis) They continue:

> [The Mantel extension test] is not a test of the appropriateness of that model: instead, it is a test for magnitude of trend given that the shape of the dose-response relation implied by the linear-logistic model is appropriate.

Similarly, J. Lee, et al., note that a number of possible dose-response models could be applied to the ETS-lung cancer data.[18] Noting the inconsistencies among the various studies in terms of the data reported, they point out that the analyst's choice of model to apply to the data can affect the conclusions:

> Any conclusions about dose response relationships should not simply be a reflection about the type of dose response model chosen by the analyst. If a linear model is fitted to data which truly have a threshold then it is highly likely that the

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> straight line will be judged to provide an adequate fit. **However this does not prove that the dose response is linear and any interpretations based on extrapolation could be quite erroneous.** (emphasis added)

Another problem with the Mantel extension test is that it does not take incremental increases in risk at **each** exposure category into account.[55] The nature of the test is such that a single increase in risk at **one** exposure category could be sufficient to produce a statistically significant test for trend. Specifically, Maclure and Greenland state:

> The heart of the dose-response hypothesis is found in the words . . . 'continuously increasing risk.' Not only does the first small dose of exposure influence risk, but additional doses further increase risk relative to the effect of the previous dose. All dose increments are hypothesized to have effects, not just one of them. **Because the extension test can yield a small p value if only one dose increment had an effect, it does not test the hypothesis of interest.**[55] (emphasis added)

Another limitation in using a test for trend was noted by J. Lee, et al., who pointed out that inclusion of the unexposed, or reference, group in the test for trend can result in a statistically significant outcome, even though the only difference is between nonexposed and exposed.[56] That is, the different exposure levels (the point of a dose-response analysis) may

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actually not be statistically significantly different from one another.

> [A]ssessment of this [dose-response] relationship should be independent of the assessment of a possible overall association, and hence . . . the **unexposed** group should be excluded from the analysis. The rationale for this exclusion is that RRs greater than unity for exposures greater than zero may not differ from each other and yet the test for trend will be significant. In this case a trend may not be present in the RR for exposures above zero. (authors' emphasis)

Thus, inclusion of the unexposed group in a test for trend can lead to an artifactual conclusion of a statistically significant trend. Moreover, because there is no error term associated with the control value (i.e., the unexposed group), the control value will have an infinite statistical impact on the reported relationship.

In a 1995 paper, Tweedie and Mengersen evaluate "dose-response," taking into account "the possible confounding effect that inclusion of the unexposed group may have."[56] In agreement with J. Lee, et al., and with Maclure and Greenland, they note that "an observed dose-response relationship may be in fact simply evidence of overall association but not of increasing (or decreasing) risk with increasing dose."

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Tweedie and Mengersen illustrate this using hypothetical data,[6] where all the risk estimates are equal at different dose levels, an exercise also carried out by Maclure and Greenland.[35] Tweedie and Mengersen also use actual data from one of the spousal smoking studies, where "we see a raised relative risk but no discernible increase of effect with increasing dose," to illustrate the same point. A "raised relative risk," as discussed later in this section, may well be due to the effects of bias and confounding; because of the nature of the test for trend, the spuriously elevated risk can lead to an improper claim of "dose-response."

Similarly, the authors of the CRS Report comment that, of the spousal smoking studies they reviewed,[44]

> All of the trend analyses include zero exposure. If the trend was linear down to zero exposure, then including that level in the trend analysis would yield the same results as when excluded. If there was a threshold effect, then a trend test which included the zero exposure level might show a trend even if an analysis which included only exposures above zero did not show such a trend. **In other words, a sharp rise at some exposure level above zero could incorrectly be interpreted as a dose response trend over all exposure levels.** (emphasis added) (p. 29)

So, if an elevated risk is reported (overall or for one exposure category), and if the nonexposed group is included in a

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test for trend, the result of the test will be statistically significant, even though risk does not increase with each increment of "dose." Thus, the use of a test for trend does not reflect dose-response, but simply the fact that, mathematically, the test is being "driven" by some reportedly elevated risk.

3. Claims of Dose-Response in the ETS Lung Cancer Studies Reflect an Increased Risk at the Highest Exposure Levels; Such Risk Estimates Do Not Reflect ETS Exposure, But Rather the Influence of Other Factors Associated with Spousal Smoking

The preceding discussion illustrates that a single elevated risk estimate can drive a so-called dose-response assessment, when a test for trend is inappropriately used to reach a conclusion about dose-response. This explanation could certainly account for the "positive" trends reported in the ETS epidemiology. As Paul Switzer, Ph.D., a statistician at Stanford University, notes:[87]

> [W]ithout the highest spousal exposure group there would be very few individual studies with statistically significant effects or significant dose-response relationships.

Why, then, are the risk estimates elevated at the highest reported spousal exposure levels? The most likely explanation relates to the fact that the elevated risk estimates are the result

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of unexplained bias and confounding. For instance, Springall writes in his submission to U.S. OSHA that data exist suggesting that spousal concordance (the tendency for smokers to marry smokers) increases with the amount smoked and therefore, "an enhanced tendency to a false dose-response exists in the presence of [smoking status] misclassification."[14] As smoking status misclassification has been adequately excluded in **none** of the spousal smoking studies, it is certainly possible that misclassification may contribute to the claimed dose-response relationships reported.[23] As noted earlier, only very small rates of smoking status misclassification could account for the risk estimates reported at high exposures by Fontham, et al.,[41] and Brownson, et al.,[43] demonstrating the clear potential for this form of bias to have an effect in this context.

Another source of bias, exposure misclassification, may also contribute to the reportedly higher risks at higher exposure levels. As the authors of the CRS Report note:[44]

> The more specific the question about exposure, the more precise the measure, **but the less accurate the recall.** That is, there is likely to be a very small error rate in reporting marriage to a smoker, but there could be a significant error in reporting actual amounts of exposure, such as numbers of cigarettes smoked by a spouse, particularly in the past. (emphasis added)

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Recall bias is also likely to produce an artificial dose-response trend in the spousal smoking data. Layard points out that cases may be motivated to try to explain their disease, which could lead to more complete recall or exaggeration of high exposure levels by cases than by controls.[18] This differential would produce apparently elevated risk estimates at high exposures. Layard also notes that, under this scenario, one would expect to see a reduction in risk (i.e., a risk estimate below 1.0) at low reported exposures, just as is seen when the data from the U.S. case-control studies on women are combined in a meta-analysis.

As noted earlier, the spousal smoking studies are not measuring ETS exposures, but rather are essentially addressing risks associated with "marriage to a smoker." Spousal smoking status carries with it a number of associated lung cancer risk factors that may be associated with amount smoked.[11]

As Layard writes:[10]

> [M]any potential confounders of reported spousal smoking-lung cancer associations, as well as smoking-status misclassification bias, are correlated with spousal smoking in a dose-dependent fashion, and such correlations could account for apparent dose-response trends.

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That is, if the effects of confounding factors and biases were indeed highest in the highest exposure group, the risk estimates for those groups would be expected to be larger. Thornton, et al., report data from their survey of risk factors in a British population that support such a relationship.[9] The highest prevalence of many of the risk factors (dietary and behavioral) they investigated was found in smokers of 20 or more cigarettes per day. This study also showed that persons exposed to ETS had higher prevalences of risk factors than did non-exposed persons. Thus, these data are strongly suggestive of a relationship such as that described by Layard.[10] As most studies of risk factor clustering have not focused on associations with amount smoked, this area requires further research. This explanation for the increased risks reported at higher spousal exposures nevertheless remains a viable one.

4. A More Rigorous Analysis of the Data Does Not Support the Dose-Response Claims that Have Been Made

In general, claims about dose-response are tenuously based on qualitative reviews of data from the spousal smoking studies. Moreover, they accept the equivalence between a positive test for trend and dose-response, which, as described herein, is inappropriate and misleading. The weakness of such claims is clearly demonstrated when Tweedie and Mengersen's more rigorous

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analysis of the "dose-response" data, published in the peer-reviewed literature, is considered.[56]

Tweedie and Mengersen's 1995 paper compares several techniques for assessing dose-response in epidemiologic studies. It includes both reanalyses of the dose-response data from the individual studies and a meta-analytic assessment. The authors comment that they "provide a more rigorous approach than the purely qualitative assessments which have often been used in the literature."[56]

As an initial step, Tweedie and Mengersen recalculate tests for dose-response for all the spousal smoking studies reporting sufficient data, using three alternate methods. The first (the Armitage method) simply tests whether the reported risks at different categories are significantly different. The authors note that its "major benefit" is that no assumption about the pattern of dose-response is made. (Since the shape of the dose-response, if any, is unknown, using models that impose a shape will influence the outcomes of the test.) The other two methods fit models, one exponential and one linear, to the data, i.e., each entails a different assumption about the nature of the dose-response. For each of the three methods, the authors perform one test **including** the unexposed group, and one test **excluding** the unexposed group.

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Tweedie and Mengersen report that when the unexposed group is **excluded**, for all three tests, only one study fits one of the models; **no other studies show a statistically significant "dose-response."** Conversely, depending on the model, when the unexposed group is included, anywhere from two to all of the studies are statistically significant (at least at the 10 percent level). Thus, these analyses illustrate the sensitivity of conclusions about dose-response to the method of analysis.

In addition to the individual-studies analysis, Tweedie and Mengersen analyze the data from the case-control studies using meta-analytic techniques. Again, three models are used, and the results differ by model and, particularly, by whether the unexposed group is included.

In conclusion, Tweedie and Mengersen note that "a simple assessment of point estimates -- without consideration of their accuracy as expressed by associated confidence intervals and without a more rigorous method of synthesising the results from individual studies -- can be quite misleading."

Overall, Tweedie and Mengersen conclude:[66]

> From the meta-analysis of studies of lung cancer and exposure to ETS in non-smoking females given here, our conclusion is that,

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despite a significant observed relative risk associated with overall exposure, there is little increase in relative risk with increasing dose. **One explanation that accounts for this somewhat unexpected situation, of an overall observed increased relative risk but little indication of positive dose response, is that some bias may be inflating all of the observed risks.** (emphasis added)

5. Conclusion: Claims About a "Dose-Response" Relationship Derived from the ETS Epidemiologic Studies Are Unfounded and Should Not Be Relied Upon by Cal/EPA

The foregoing discussion clearly illustrates that the claims that data in some of the epidemiologic studies on spousal smoking and lung cancer support a dose-response relationship are based on a misinterpretation of the use and meaning of statistical tests for trends. Positive trend results can be explained due to spuriously elevated risk estimates arising from uncontrolled confounding and biases. Moreover, the results of more appropriate, more rigorous statistical analyses reveal inconsistencies among and within studies in terms of "dose-response." Because so many questions remain, "dose-response" claims should not be used by Cal/EPA to support its analysis of ETS.

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